```
=> file medline, caplus,scisearch,lifesci,biosis,embase
=> s cpla2 or cytosolic phospholipase A2
TOTAL FOR ALL FILES
L7        3723 CPLA2 OR CYTOSOLIC PHOSPHOLIPASE A2

=> s e. c. 3.1.1.4 or ec 3.1.1.4
TOTAL FOR ALL FILES
L14       1777 E. C. 3.1.1.4 OR EC 3.1.1.4

=> s l7 or l14
TOTAL FOR ALL FILES
L21       5485 L7 OR L14

=> s l21 and (x-ray or crystal?)
TOTAL FOR ALL FILES
L28        114 L21 AND (X-RAY OR CRYSTAL?)

=> s l28 not 2000-2001/py
TOTAL FOR ALL FILES
L35        101 L28 NOT 2000-2001/PY

=> dup rem l35
PROCESSING COMPLETED FOR L35
L36          73 DUP REM L35 (28 DUPLICATES REMOVED)

=> focus l36
PROCESSING COMPLETED FOR L36
L37          73 FOCUS L36 1-

=> d ibib abs 1-73

L37  ANSWER 1 OF 73  CAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:        1999:2229  CAPLUS
DOCUMENT NUMBER:         130:164235
TITLE:                   Crystallization and preliminary X-
                         ray diffraction studies of piratoxin II, a
                         phospholipase A2 isolated from the venom of Bothrops
                         pirajai
AUTHOR(S):               Lee, W.-H.; Goncalez, M. C.; Ramalheira, R. M. F.;
                         Kuser, P. R.; Toyama, M. H.; Oliveira, B.; Giglio, J.
                         R.; Marangoni, S.; Polikarpov, I.
CORPORATE SOURCE:        Laboratorio Nacional de Luz Sincrotron, Sao Paulo,
                         13083-970, Brazil
SOURCE:                  Acta Crystallogr., Sect. D: Biol. Crystallogr. (1998),
                         D54(6, Pt. 2), 1437-1439
                         CODEN: ABCRE6; ISSN: 0907-4449
PUBLISHER:               Munksgaard International Publishers Ltd.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   The phospholipases A2 (PLA2, E.C. 3.
     1.1.4, phosphatide sn2 acylhydrolases) are the
     major components of the venom of several snakes.  They are responsible for
     several important pharmacol. effects obsd. in ophidian incidents.  PLA2
     piratoxin II from Bothrops pirajai has been crystd. by the
     vapor-diffusion technique.  X-ray diffraction data
     have been collected to 2.04 .ANG. resoln. (90.2% complete, Rmerge =
     0.070).  The space group is P21 and the cell parameters are a = 46.19, b =
     60.36, c = 58.74 .ANG. and .beta. = 96.05.degree..  The structure has been
     solved by mol. replacement using the crystallog. structure of
     PLA2 from Bothrops asper (PDB code 1CLP) as a search model.
REFERENCE COUNT:         24
REFERENCE(S):            (1) Arni, R; Acta Cryst 1995, VD51, P311 CAPLUS
                         (2) Deenen, L; Biochem Biophys Acta 1963, V70, P538
                             CAPLUS
                         (3) Dennis, E; J Biol Chem 1994, V269, P13057 CAPLUS
                         (4) Diaz, C; Biochem Biophys Acta 1991, V1070, P455
                             CAPLUS
                         (5) Gutierrez, J; Toxicon 1995, V33, P1405 CAPLUS
                         ALL CITATIONS AVAILABLE IN THE RE FORMAT
```

L37 ANSWER 2 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1981:231586 BIOSIS
DOCUMENT NUMBER: BA72:16570
TITLE: PH DEPENDENCE OF THE BINDING CONSTANT OF CALCIUM TO COBRA VENOM PHOSPHO LIPASES A-2 **EC-3.1.1.4.**
AUTHOR(S): TESHIMA K; IKEDA K; HAMAGUCHI K; HAYASHI K
CORPORATE SOURCE: DEP. BIOL., FAC. SCI., OSAKA UNIV., TOYONAKA, OSAKA 560.
SOURCE: J BIOCHEM (TOKYO), (1981) 89 (1), 13-20.
CODEN: JOBIAO. ISSN: 0021-924X.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB The pH dependence of the binding constant of Ca2+ to phospholipases A2 [**EC 3.1.1.4**] of Naja naja siamensis, N. naja kaouthia and N. naja atra was studied at an ionic strenth of 0.1 and 25.degree. C by measuring the decrease in tryptophyl fluorescence. All 3 enzymes exhibited precisely the same pH dependence. The binding constants at various pH values of the enzyme of N. naja naja, reported previously, fell practically on the present pH dependence curve. The pK value of an ionizable group was perturbed from 7.55-7.25 and protonation of another group with a pK value of 5.4 competed with the binding of the Ca2+ ion. The former group was assigned as a His residue corresponding to His 48 and the latter as Asp 49 in the active site on the basis of **X-ray crystallographic** results on the bovine pancreas enzyme. The pH dependence curve for porcine pancreas phospholipase A2, which was reported previously but is not yet well understood, was analyzed in a similar way on the basis of th pK value of His 48 estimated from the pH dependence of the trypotphyl fluorescence. The data were well interpreted in terms of pK shifts of the .alpha.-amino group from 8.4-7.9 and of His 48 from 6.6-5.6 and in terms of protonation of Asp 49 with a pK value of 5.35, which competes with the Ca2+ ion binding. The pK shift of His 48 is in good agreement with those reported recently for equine and bovine enzymes. The pH dependences of fluorescence intensity at 350 nm (excited at 290 nm) of a cobra phospholipase A2 of N. naja siamensis and its complex with Ca2+ were studied at an ionic strength of 0.1 and 25.degree. C. Two other cobra enzymes also showed similar pH dependences. The curves were well interpreted in terms of participations of groups with pK values less than 2, 3.9, 9.75 and 11.1, in addition to the contributions from Asp 49 and His 48 perturbed by the Ca2+ binding.

L37 ANSWER 3 OF 73 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1977:152042 CAPLUS
DOCUMENT NUMBER: 86:152042
TITLE: Structure of porcine pancreatic prephospholipase A2
AUTHOR(S): Drenth, J.; Enzing, C. M.; Kalk, K. H.; Vessies, J. C. A.
CORPORATE SOURCE: Lab. Struct. Chem., Groningen, Neth.
SOURCE: Nature (London) (1976), 264(5584), 373-7
CODEN: NATUAS
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Crystal** structure detns. on porcine pancreatic prephospholipase A2 (I) showed that I has the shape of a rectangular box 25 .times. 28 .times. 35 .ANG. which contains neither regular .alpha.-helixes nor .beta.-pleated sheets, and only 2 regions of distorted helix conformation, residues 11-17 and 36-41. Of the 7 disulfide bridges, 4 were in a plane through the middle of the mol. and 3 at the mol. surface. The Arg7-Ala8 bond, which splits during activation of I by trypsin, was also located in an exposed position on the surface of the mol. The mol. model for I suggested a binding mode for monomers of substrate which involves arginine at position 108 and the Ca ion located in this region of the **crystal**. A mechanism for the esterase activity of phospholipase A2 (**EC 3.1.1.4**) was predicted from a comparison with other ester-splitting enzymes.

L37 ANSWER 4 OF 73 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:162654 CAPLUS
DOCUMENT NUMBER: 102:162654
TITLE: Gas chromatographic determination of phospholipase A2 activity
AUTHOR(S): Nuhn, P.; Heine, L.; Benecke, R.

CORPORATE SOURCE: Sekt. Pharm., Martin-Luther-Univ., Halle/Saale, 4020, Ger. Dem. Rep.
SOURCE: Zentralbl. Pharm., Pharmakother. Laboratoriumsdiagn. (1985), 124(2), 77-81
CODEN: ZPPLBF; ISSN: 0049-8696
DOCUMENT TYPE: Journal
LANGUAGE: German

AB Test curves for the amt. of palmitic acid released from dipalmitoylphosphatidylcholine (I) by phospholipase A2 (**EC 3.1.1.4**) were constructed based on gas chromatog. sepn. of the fatty acid, with myristic acid as an internal std. The enzyme used was either purified from snake venom or was a **cryst**. snake venom prepn. from Vipera ammodytes. The curves showed linearity of the relation between peak height and amt. of fatty acid when both were expressed as a ratio with a known amt. of myristic acid. The fatty acids were converted to their Me esters before gas chromatog. The pH optimum was 7.5 for this assay, and the optimum enzyme concn. was 20 .mu.g **cryst**. snake venom and 10 .mu.g phospholipase A2 per mL test soln. The dependence of fatty acid released on I concn. was also shown. DMF at 10% caused an increase in substrate turnover rate produced by the enzyme (0.115 vs. 0.108 mg/mL palmitate), whereas 20% DMF decreased the rate due to denaturation of the enzyme. Addn. of 10% DMF to the lipid substrate suspension before sonication (corresponding to a final concn. of 1% DMF in the test soln.) caused a rate (0.085 mg/mL palmitate) that was lower than that of controls.

L37 ANSWER 5 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1976:211090 BIOSIS
DOCUMENT NUMBER: BA62:41090
TITLE: ENZYMATIC PROBES OF LIPO PROTEIN STRUCTURE HYDROLYSIS OF HUMAN SERUM LOW DENSITY LIPO PROTEIN 2 BY PHOSPHO LIPASE A-2 **EC-3.1.1.4**.
AUTHOR(S): AGGERBECK L P; KEZDY F J; SCANU A M
SOURCE: J BIOL CHEM, (1976) 251 (12), 3823-3830.
CODEN: JBCHA3. ISSN: 0021-9258.
FILE SEGMENT: BA; OLD
LANGUAGE: Unavailable

AB Pure phospholipase A2 (**EC 3.1.1.4**) from Crotalus atrox is able to hydrolyze all the phosphatidylcholine, phosphatidylserine, and phosphatidylethanolamine of human serum low density lipoprotein (LDL2). In accord with the substrate specificity of the enzyme, sphingomyelin, other minor lipids and proteins are not hydrolyzed. The enzyme-modified particles remain water-soluble and, upon reisolation, contain all of the lysophospholipids and free fatty acids produced during the reaction. By EM, circular dichroic, analytical ultracentrifugal, immunologic, and small angle **X-ray** scattering techniques, the enzyme-modified particles exhibit only modest changes when compared with native LDL2. Accumulation of negative charges on the lipoprotein during hydrolysis results in the repression of ionization of the free fatty acid products. This electrostatic effect can be analyzed in terms of the Linderstrom-Lang model which yields an equivalent spherical radius of .apprx. 100 .ANG. for the particles. For the substrate concentration range of 2 .div. 100 .times. 10-4 M hydrolyzable phospholipid, the kinetics of formation of fatty acids (P) obey the equation .**GRAPHIC**. with kcat/Km = 1.3 .times. 105 M-1s-1 and Kp .simeq. 3 .times. 10-4 M. Serum albumin relieves the competitive product inhibition and leads to an apparent first order rate law. Albumin removes virtually all of the free fatty acids and up to 30% of the lysophospholipid products without a significant effect on the stability and structural properties of the enzyme-modified LDL2. Phospholipase A2 hydrolyzable phospholipids are probably located at the surface of the LDL2 particle and are in a fluid state. Hydrolysis by phospholipase A2 causes no significant changes in the basic structural features of the particle even after the partial loss of free fatty acids and lysophospholipids to albumin. The availability of stable and well characterized LDL2 derivatives may be useful for further studies aimed at an understanding of the mode by which proteins and lipids interact in lipoproteins.

L37 ANSWER 6 OF 73 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1980:490831 CAPLUS

DOCUMENT NUMBER: 93:90831
TITLE: Comparison of a relatively toxic phospholipase A2 from Naja nigricollis snake venom with that of a relatively nontoxic phospholipase A2 from Hemachatus haemachatus snake venom. I. Enzymatic activity on free and membrane-bound substrates
AUTHOR(S): Condrea, Eleonora; Yang, Chen-Chung; Rosenberg, Philip
CORPORATE SOURCE: Sect. Pharmacol. Toxicol., Univ. Connecticut, Storrs, CT, 06268, USA
SOURCE: Biochem. Pharmacol. (1980), 29(11), 1555-63
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
AB When compared on purified egg L-.alpha.-phosphatidylcholine basic phospholipase A2 (**EC 3.1.1.4**) (I) from N. nigricollis and neutral I from H. haemachatus showed similar pH- and temp.-dependence and were equally affected by activators and inhibitors. The Vmax values of 250 and 1052 microequiv/min/mg and Km values of 4.2 and 2.2 mM were obtained for basic and neutral I, resp., and both enzymes favored the substrates in the liq. **cryst**. state. Using a buffered egg yolk diln. as substrate, Vmax values of 356 and 616 microequiv./min/mg and Km values of 29 and 25 nM were obtained for basic and neutral I, resp. Basic and neutral I also differed in their ability to hydrolyze phospholipid substrates, either alone, or in various combinations. No difference was obsd. between the actions of basic and neutral I on fresh human erythrocytes, whereas erythrocytes from stored, outdated blood were hemolyzed and phospholipids were fully hydrolyzed by basic I, but neutral I was nonhemolytic and caused only limited hydrolysis. Comparison of hydrolysis in permeable red cell ghosts and in Triton-solubilized membranes by the enzymes showed that the high preference of basic I for phosphatidylserine was masked by sequestration.

L37 ANSWER 7 OF 73 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1974:549509 CAPLUS
DOCUMENT NUMBER: 81:149509
TITLE: Effect of phospholipases A and C on free amino acid content of the squid axon
AUTHOR(S): Rosenberg, P.; Khairallah, E. A.
CORPORATE SOURCE: Sch. Pharm., Univ. Connecticut, Storrs, Conn., USA
SOURCE: J. Neurochem. (1974), 23(1), 55-64
CODEN: JONRA9
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phospholipase A (**EC 3.1.1.4**) caused a much greater redn. in the free amino acid content of the axoplasm and sheath of squid axonal prepns. than did phospholipase C (EC 3.1.4.3), even when phospholipase A was used at concns. causing less phospholipid splitting. Phospholipase A also caused a much greater concomitant increase in amino acids released into the incubation medium. The loss of amino acids was considered to be a sensitive indicator of the effects of disrupting hydrophobic and hydropholic bonds between phospholipids and proteins in the membrane. Since the hydrolytic actions of phospholipases A and C primarily affect hydrophobic and hydrophilic bonding, resp., the disruption of hydrophobic bonding apparently has a much greater effect on the structure of the nonlipid portion of the axonal membranes than does disruption of hydrophilic assocns. This does not support the unit membrane hypothesis for membrane structure, but the results can be interpreted in terms of the protein-**crystal** or fluid mosaic models.

L37 ANSWER 8 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1978:139503 BIOSIS
DOCUMENT NUMBER: BA65:26503
TITLE: CIRCULAR DICHROISM OF PORCINE BOVINE AND EQUINE PANCREATIC PHOSPHO LIPASE A-2 **EC-3.1.1.4** AND THEIR ZYMOGENS UNUSUAL CONFORMATIONS SIMULATING HELIX CONTENT.
AUTHOR(S): JIRGENSONS B; DE HAAS G H
CORPORATE SOURCE: DEP. BIOCHEM., UNIV. TEX. SYST. CANCER CENT., M.D. ANDERSON HOSP. TUMOR INST., HOUSTON, TEX. 77030, USA.

SOURCE: BIOCHIM BIOPHYS ACTA, (1977) 494 (2), 285-292.
CODEN: BBACAQ. ISSN: 0006-3002.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Conformation of porcine, bovine, and equine pancreatic phospholipases A2 (**EC 3.1.1.4**) and their zymogens was studied by the circular dichroism (CD) probe in the far and near UV spectral zones. All these phospholipases and their zymogens displayed CD curves suggesting the presence of moderate amounts of .alpha.-helical conformation. On the basis of known primary structure and recent **X-ray** structural analysis of prophospholipase A2 **crystals** it had to be concluded that the positive CD band centered at 190-191 nm and the negative bands located at 208-210 nm and 222-225 nm, respectively, was caused not only by .alpha.-helics but also by other symmetric structures, probably rings containing disulfide bonds. The main chain conformation of the phospholipases and their zymogens was found very resistant to acid but it was sensitive to sodium dodecyl sulfate in acid solutions and, to a lesser extent, to alkali. According to the observed CD changes in the presence of perturbants, the stability of the macromolecules of these proteins was determined chiefly by the difulfide bonds and hydrophobic interactions. The CD spectra in the near UV zone showed that the differences between the enzymes and their zymogens, with respect to the tertiary structure, were very small. Also it was observed that the tertiary structure of the horse phospholipase differed from the tertiary structure of the porcine and bovine phospholipases. The tertiary structure of all these enzymes and zymogens was very sensitive to sodium dodecyl sulfate.

L37 ANSWER 9 OF 73 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1972:97607 CAPLUS
DOCUMENT NUMBER: 76:97607
TITLE: Structure of an abnormal plasma lipoprotein (LP-X) characterizing obstructive jaundice
AUTHOR(S): Seidel, D.; Agostini, B.; Mueller, P.
CORPORATE SOURCE: Med. Universitaetsklin., Heidelberg, Ger.
SOURCE: Biochim. Biophys. Acta (1972), 260(1), 146-52
CODEN: BBACAQ
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The structure of the abnormal plasma lipoprotein (LP-X) characterizing obstructive jaundice was studied by electron microscopy and immunol. In the electron microscope, neg. stained prepns. of LP-X appear to consist of round particles of 300-700 .ANG. with a tendency to aggregate and to undergo marked structural changes. Studies with specific antibodies following phospholipase A2 (**EC 3.1.1.4**) treatment indicate the presence of apolipoprotein X on the surface and of albumin in the core of the particles. De-naturation of the particles with phospholipase A2 also suggests the presence of phospholipids on the surface, which is in agreement with the results obtained by **x-ray** diffraction anal.

L37 ANSWER 10 OF 73 MEDLINE
ACCESSION NUMBER: 1999192701 MEDLINE
DOCUMENT NUMBER: 99192701 PubMed ID: 10089531
TITLE: **Crystallization** and preliminary **X-ray** diffraction studies of piratoxin II, a phospholipase A2 isolated from the venom of Bothrops pirajai.
AUTHOR: Lee W; Goncalez M C; Ramalheira R M; Kuser P R; Toyama M H; Oliveira B; Giglio J R; Marangoni S; Polikarpov I
CORPORATE SOURCE: Laboratorio Nacional de Luz Sincrotron, Caixa Postal 6192, 13083-970 Campinas, Sao Paulo, Brazil.
SOURCE: ACTA CRYSTALLOGRAPHICA. SECTION D: BIOLOGICAL CRYSTALLOGRAPHY, (1998 Nov 1) 54 (2 (Pt 6)) 1437-9.
Journal code: C3C; 9305878. ISSN: 0907-4449.
PUB. COUNTRY: Denmark
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990614

Last Updated on STN: 19990614
Entered Medline: 19990601

AB The phospholipases A2 (PLA2, **E.C. 3.1.1.4**, phosphatide sn2 acylhydrolases) are the major components of the venom of several snakes. They are responsible for several important pharmacological effects observed in ophidian incidents. PLA2 piratoxin II from Bothrops pirajai has been **crystallized** by the vapour-diffusion technique. **X-ray** diffraction data have been collected to 2.04 A resolution (90.2% complete, Rmerge = 0.070). The space group is P21 and the cell parameters are a = 46.19, b = 60.36, c = 58.74 A and beta = 96.05 degrees. The structure has been solved by molecular replacement using the **crystallographic** structure of PLA2 from Bothrops asper (PDB code 1CLP) as a search model.

L37 ANSWER 11 OF 73 MEDLINE
ACCESSION NUMBER: 1999263344 MEDLINE
DOCUMENT NUMBER: 99263344 PubMed ID: 10329793
TITLE: **Crystallization** and preliminary **X-ray** diffraction studies of piratoxin III, a D-49 phospholipase A2 from the venom of Bothrops pirajai.
AUTHOR: Lee W H; Toyama M H; Soares A M; Giglio J R; Marangoni S; Polikarpov I
CORPORATE SOURCE: Laboratorio Nacional de Luz Sincrotron, Caixa Postal 6192, CEP 13083-970, Campinas SP, Brazil.
SOURCE: ACTA CRYSTALLOGRAPHICA. SECTION D: BIOLOGICAL CRYSTALLOGRAPHY, (1999 Jun) 55 (Pt 6) 1229-30.
Journal code: C3C; 9305878. ISSN: 0907-4449.
PUB. COUNTRY: Denmark
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990827
Last Updated on STN: 20000303
Entered Medline: 19990813

AB Piratoxin III (PrTX-III) is a phospholipase A2 (PLA2, **E.C. 3.1.1.4**, phosphatide sn-2 acylhydrolase) isolated from Bothrops pirajai. **Crystals** of PrTX-III were obtained using the vapour-diffusion technique and **X-ray** diffraction data have been collected to 2.7 A resolution. The enzyme was **crystallized** in the space group C2 with unit-cell parameters a = 60.88, b = 100.75, c = 48.19 A, beta = 123. 89 degrees. A molecular-replacement solution of the structure has been found using bothropstoxin I from the venom of B. jararacussu as a search model.

L37 ANSWER 12 OF 73 MEDLINE
ACCESSION NUMBER: 1999251533 MEDLINE
DOCUMENT NUMBER: 99251533 PubMed ID: 10319815
TITLE: **Crystal** structure of human **cytosolic phospholipase A2** reveals a novel topology and catalytic mechanism.
AUTHOR: Dessen A; Tang J; Schmidt H; Stahl M; Clark J D; Seehra J; Somers W S
CORPORATE SOURCE: Biochemistry, Wyeth Research, Cambridge, Massachusetts 02140, USA.. adessen@genetics.com
SOURCE: CELL, (1999 Apr 30) 97 (3) 349-60.
Journal code: CQ4; 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1CJY
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 19990601
Entered Medline: 19990520

AB **Cytosolic phospholipase A2** initiates the biosynthesis of prostaglandins, leukotrienes, and platelet-activating factor (PAF), mediators of the pathophysiology of asthma and arthritis. Here, we report the **X-ray crystal** structure of human **cPLA2** at 2.5 A. **cPLA2** consists of an

N-terminal calcium-dependent lipid-binding/C2 domain and a catalytic unit whose topology is distinct from that of other lipases. An unusual Ser-Asp dyad located in a deep cleft at the center of a predominantly hydrophobic funnel selectively cleaves arachidonyl phospholipids. The structure reveals a flexible lid that must move to allow substrate access to the active site, thus explaining the interfacial activation of this important lipase.

L37 ANSWER 13 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 92:473536 SCISEARCH
THE GENUINE ARTICLE: JG734
TITLE: REGULATION OF EXTRACELLULAR PHOSPHOLIPASE-A2 ACTIVITY - IMPLICATIONS FOR INFLAMMATORY DISEASES
AUTHOR: MUKHERJEE A B (Reprint); CORDELLAMIELE E; MIELE L
CORPORATE SOURCE: NICHHD, HUMAN GENET BRANCH, DEV GENET SECT, BLDG 10, ROOM 95242, BETHESDA, MD, 20892 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: DNA AND CELL BIOLOGY, (APR 1992) Vol. 11, No. 3, pp. 233-243.
ISSN: 1044-5498.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 58

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Phospholipases A2(PLA2s; **E.C. 3.1.1.4**) are a family of esterases that are involved in myriads of physiological and pathological processes. The involvement of these enzymes, especially the extracellular PLA2S, in the generation of proinflammatory lipid mediators makes them a very important target for investigation. These PLA2s have been suggested to be involved in the pathogenesis of several human inflammatory diseases. Thus, delineating the mechanism(s) of regulation of the activity of these enzymes may provide a better understanding of the pathophysiology of these diseases and allow the rational design and development of novel therapeutic agents. In this article, we provide a brief description of PLA2S in general with a special emphasis on extracellular enzymes, their mechanism(s) of action, and possible role in the pathogenesis of inflammatory diseases. Additionally, we describe: (i) a novel mechanism of activation of extracellular PLA2s by transglutaminases and (ii) the development of one class of antiinflammatory agents, antiflammatory, derived from the active site structure of endogenous PLA2-inhibitory proteins.

L37 ANSWER 14 OF 73 MEDLINE
ACCESSION NUMBER: 1998104145 MEDLINE
DOCUMENT NUMBER: 98104145 PubMed ID: 9430701
TITLE: **Crystal** structure of a calcium-phospholipid binding domain from **cytosolic phospholipase A2**.
AUTHOR: Perisic O; Fong S; Lynch D E; Bycroft M; Williams R L
CORPORATE SOURCE: Medical Research Council Laboratory of Molecular Biology, Medical Research Council Centre, Cambridge, United Kingdom.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Jan 16) 273 (3) 1596-604.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980224
Last Updated on STN: 19980224
Entered Medline: 19980212

AB **Cytosolic phospholipase A2** (**cPLA2**) is a calcium-sensitive 85-kDa enzyme that hydrolyzes arachidonic acid-containing membrane phospholipids to initiate the biosynthesis of eicosanoids and platelet-activating factor, potent inflammatory mediators. The calcium-dependent activation of the enzyme is mediated by an N-terminal C2 domain, which is responsible for calcium-dependent translocation of the enzyme to membranes and that enables the intact enzyme to hydrolyze membrane-resident substrates. The 2.4-A **x-**

ray crystal structure of this C2 domain was solved by multiple isomorphous replacement and reveals a beta-sandwich with the same topology as the C2 domain from phosphoinositide-specific phospholipase C delta 1. Two clusters of exposed hydrophobic residues surround two adjacent calcium binding sites. This region, along with an adjoining strip of basic residues, appear to constitute the membrane binding motif. The structure provides a striking insight into the relative importance of hydrophobic and electrostatic components of membrane binding for **cPLA2**. Although hydrophobic interactions predominate for **cPLA2**, for other C2 domains such as in "conventional" protein kinase C and synaptotagmins, electrostatic forces prevail.

L37 ANSWER 15 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1984:353741 BIOSIS
DOCUMENT NUMBER: BA78:90221
TITLE: ROLE OF THE AMINO TERMINUS IN THE INTERACTION OF PANCREATIC PHOSPHO LIPASE A-2 **EC-3.1.1.4** WITH AGGREGATED SUBSTRATES PROPERTIES AND **CRYSTAL** STRUCTURE OF TRANS AMINATED PHOSPHO LIPASE A-2.
AUTHOR(S): DIJKSTRA B W; KALK K H; DRENTH J; DE HAAS G H; EGMOND M R; SLOTBOOM A J
CORPORATE SOURCE: LAB. BIOCHEM., STATE UNIV. UTRECHT, TRANSITORIUM 3, UNIV. CENTER "DE UITHOF", PADUALAAN 8, 3508 TB UTRECHT, NETH.
SOURCE: BIOCHEMISTRY, (1984) 23 (12), 2759-2766.
CODEN: BICHAW. ISSN: 0006-2960.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB A free N-terminal .alpha.-NH3+ group is absolutely required for full catalytic activity of phospholipase A2 on aggregated substrates. To elucidate how this .alpha.-NH3+ group triggers catalytic activity, this group was specifically transaminated in various pancreatic phospholipases A2. Porcine, porcine iso-, equine, human, ovine and bovine phospholipases A2 all lose catalytic activity on micellar substrates due to the inability of the transminated proteins to bind to neutral micellar substrate analogs, as was found for the zymogens. Loss of activity is pseudo 1st order, the rate constants being different for the enzymes studied. The transaminated phospholipases A2 have an intact active site, as catalytic activities on monomeric substrates are comparable to those of the respective zymogens. The **X-ray** structure of transaminated bovine phospholipase A2 at 2.1-.ANG. resolution shows that the N-terminal region and the sequence 63-72 in this protein are more flexible than in the native enzyme. Also, in this respect, the transaminated enzyme very much resembles the zymogen structure. In good agreement with this, it was found by photochemically-induced dynamic nuclear polarization 1H NMR that aromatic resonances of Trp-3 and Tyr-69 are affected by transamination. In addition, fluorescence spectroscopy of the unique Trp-3 in transaminated bovine phospholipase A2 revealed a red shift of the emission maximum indicative of a more polar environment of Trp-3 in the transaminated phospholipase A2 as compared to the enzyme. The high mobility or disorder of the N-terminal region and of the 63-72 region is due to disruption of the H bonds of the .alpha.-NH3+ with the O.epsilon.1 atom of Gln-4 and the carbonyl oxygen of Asn-71 by transamination. This increased mobility or disorder destroys affinity for aggregated phospholipids or, depending on the nature of the phospholipids, leads to unproductive binding.

L37 ANSWER 16 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1980:175141 BIOSIS
DOCUMENT NUMBER: BA69:50137
TITLE: PROTON NMR PH TITRATION STUDIES OF THE HISTIDINES OF PANCREATIC PHOSPHO LIPASE A-2 **EC-3.1.1.4**.
AUTHOR(S): AGUIAR A; DE HAAS G H; JANSEN E H J M; SLOTBOOM A J; WILLIAMS R J P
CORPORATE SOURCE: INORG. CHEM. LAB., UNIV. OXFORD, S. PARKS RD., OXFORD OX1 3QR, ENGL., UK.
SOURCE: EUR J BIOCHEM, (1979) 100 (2), 511-518.
CODEN: EJBCAI. ISSN: 0014-2956.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB A study using 1H NMR of the histidines of phospholipase A2 isolated from porcine, bovine and equine pancreas is reported. Assignment of histidine resonances was achieved by comparison of different enzymes and use of paramagnetic probes. pH titration curves for various histidyl resonances were obtained and compared in the presence and absence of Ca. Ca lowers the pKa of the active site histidine. NMR results are compared with the known **X-ray** 3-dimensional structure for the bovine enzyme.

L37 ANSWER 17 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1984:306281 BIOSIS
DOCUMENT NUMBER: BA78:42761
TITLE: DIFFERENT EFFECTS OF SUBSTITUTION OF THE NEAR INVARIANT GLUTAMINE 4 ON THE PROPERTIES OF PORCINE AND BOVINE PANCREATIC PHOSPHO LIPASES A-2 **EC-3**. **1.1.4**.
AUTHOR(S): VAN SCHARRENBURG G J M; PUIJK W C; SEEGER P R; DE HAAS G H; SLOTBOOM A J
CORPORATE SOURCE: LABORATORY OF BIOCHEMISTRY, STATE UNIVERSITY OF UTRECHT, UNIVERSITY CENTRE DE UITHOF, PADUALAAN 8, 3584 CH UTRECHT, NETHERLANDS.
SOURCE: BIOCHEMISTRY, (1984) 23 (6), 1256-1263.
CODEN: BICHAW. ISSN: 0006-2960.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The precise role of the near-invariant Gln-4 residue in bovine and porcine pancreatic phospholipases A2 was investigated with semisynthesis. Both in bovine and in porcine .epsilon.-amidinated phospholipases A2, Gln-4 was substituted by Glu, Asn and Nle. Binding and kinetic experiments revealed that replacement of Gln-4 by Asn or Nle in bovine phospholipase A2 eliminates most of the activity, whereas a Gln-4 .fwdarw. Glu substitution affects the enzymatic activity but not the affinity for neutral aggregated substrates. The absolute requirement of an O.epsilon.1 function of Gln or Glu at the 4-position in bovine phospholipase A2 for a functional lipid binding domain is indicated. In contrast, all the porcine phospholipase A2 mutants show affinities for micellar aggregates comparable to that of the native enzyme and possess almost full catalytic activity in the kinetic assays with micellar and monomeric short-chain lecithins. The opposite effect\of the substitution of Gln-4 by Nle or Asn on the properties of the 2 enzymes is most likely a result of the presence of a Glu residue at position 71 in the porcine enzyme, instead of an Asn as in the bovine enzyme. The porcine phospholipase A2 is known to possess a 2nd Ca2+ binding site, located at Glu-71 and affecting the N-terminal region. Recent **X-ray** data of bovine and porcine phospholipases A2, showing different conformations of the peptide loop 59-71 in these 2 enzymes, are in good agreement with this explanation.

L37 ANSWER 18 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1982:156944 BIOSIS
DOCUMENT NUMBER: BA73:16928
TITLE: THE 2.5 ANGSTROM **CRYSTAL** STRUCTURE OF A DIMERIC PHOSPHO LIPASE A-2 **EC-3.1**. **1.4** FROM THE VENOM OF CROTALUS-ATROX.
AUTHOR(S): KEITH C; FELDMAN D S; DEGANELLO S; GLICK J; WARD K B; JONES E O; SIGLER P B
CORPORATE SOURCE: DEP. OF PHARMACOLOGY, NEW YORK UNIVERSITY MEDICAL CENTER, 550 FIRST AVENUE, NEW YORK, N.Y. 10016.
SOURCE: J BIOL CHEM, (1981) 256 (16), 8602-8607.
CODEN: JBCHA3. ISSN: 0021-9258.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The **crystal** structure of the dimeric (.alpha.2) phospholipase A2 from C. atrox was determined by multiple isomorphous replacement to 2.5 .ANG. resolution. A skeletal model was fit to the electron density, and the stereochemistry of the backbone was idealized. The dimeric molecule is a well-defined oblate ellipsoid composed of 2 covalently identical subunits related by a local dyad axis which is essentially exact except for deviations at the periphery induced by ionic lattice contacts with neighboring dimers. As expected, the basic architecture of the individual protomers is similar to the structure of the homologous monomeric bovine enzyme. The intramolecular contact surface between the protomers is

extensive and involves the catalytic and Ca-binding sites. Access to an internal cavity formed by the enclosed and abutting active center regions is quite restricted. The putative interfacial recognition surfaces of each protomer are exposed to the solvent but are on opposing surfaces of the ellipsoid, suggesting that both of these regions cannot interact with the same membrane surface simultaneously unless the membrane is distorted from planarity and/or the dimer is significantly modified.

L37 ANSWER 19 OF 73 MEDLINE
ACCESSION NUMBER: 1998332749 MEDLINE
DOCUMENT NUMBER: 98332749 PubMed ID: 9665851
TITLE: Solution structure and membrane interactions of the C2 domain of **cytosolic phospholipase A2**.
AUTHOR: Xu G Y; McDonagh T; Yu H A; Nalefski E A; Clark J D; Cumming D A
CORPORATE SOURCE: Small Molecule Drug Discovery, Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA.
SOURCE: JOURNAL OF MOLECULAR BIOLOGY, (1998 Jul 17) 280 (3) 485-500.
Journal code: J6V; 2985088R. ISSN: 0022-2836.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1BCI
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980820
Last Updated on STN: 19980820
Entered Medline: 19980807

AB The amino-terminal, 138 amino acid C2 domain of **cytosolic phospholipase A2** (**cPLA2**-C2) mediates an initial step in the production of lipid mediators of inflammation: the Ca2+-dependent translocation of the enzyme to intracellular membranes with subsequent liberation of arachidonic acid. The high resolution solution structure of this Ca2+-dependent, lipid-binding domain (CaLB) has been determined using heteronuclear three-dimensional NMR spectroscopy. Secondary structure analysis, derived from several sets of spectroscopic data, shows that the domain is composed of eight antiparallel beta-strands with six interconnecting loops that fits the "type II" topology for C2 domains. Using a total of 2370 distance and torsional restraints, the structure was found to be a beta-sandwich in the "Greek key" motif. The solution structure of **cPLA2**-C2 domain is very similar to the **X-ray crystal** structure of the C2 domain of phospholipase-C-delta and phylogenetic analysis clarifies the structural role of highly conserved residues. Calorimetric studies further demonstrate that **cPLA2**-C2 binds two Ca2+ with observed Kds of approximately 2 microM in an entropically assisted process. Moreover, regions on **cPLA2**-C2 interacting with membranes were identified by 15N-HSQC-spectroscopy of **cPLA2**-C2 in the presence of low molecular weight lipid micelles. An extended binding site was identified that binds the phosphocholine headgroup in a Ca2+-dependent manner and also interacts with proximal regions of the membrane surface. Based upon these results, a structural model is presented for the mechanism of association of **cPLA2** with its membrane substrate.
Copyright 1998 Academic Press.

L37 ANSWER 20 OF 73 MEDLINE
ACCESSION NUMBER: 77134745 MEDLINE
DOCUMENT NUMBER: 77134745 PubMed ID: 191065
TITLE: Recognition of different pools of phosphatidylglycerol in intact cells and isolated membranes of Acholeplasma laidlawii by phospholipase A2.
AUTHOR: Bevers E M; Singal S A; Op den Kamp J A; van Deenen L L
SOURCE: BIOCHEMISTRY, (1977 Apr 5) 16 (7) 1290-5.
Journal code: A0G; 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197705

ENTRY DATE: Entered STN: 19900313
Last Updated on STN: 19970203
Entered Medline: 19770527

AB Phospholipase A2 (**EC 3.1.1.4**) from pig pancreas hydrolyzes phosphatidylglycerol in intact cells and isolated membranes of Acholeplasma laidlawii. Complete degradation of phosphatidylglycerol in intact cells at 37 degrees C does not result in lysis as shown by the retention of intracellular K+ ions and the cytoplasmic glucose-6-phosphatase, as well as the inability to detect activity of membrane-bound intracellular NADH-oxidase. A. laidlawii was grown on linoleic acid. Phospholipase A2 treatment of these cells at 5 degrees C, at which temperature the lipids are still in the liquid-**crystalline** state, results in a rapid breakdown of 50% of the phosphatidylglycerol. The residual phosphatidylglycerol can be hydrolyzed only at elevated temperatures and at much smaller rates, depending strongly on the incubation temperature. When membranes isolated from these cells are incubated at 5 degrees C, 70% of the phosphatidylglycerol is hydrolyzed immediately. The hydrolysis of the residual 30% is again strongly temperature dependent. Cells were grown on palmitate, elaidate, or oleate to investigate possible effects of the lipid phase transition on the accessibility of phosphatidylglycerol for phospholipase A2. Under conditions in which all the lipid is in the solid state, no hydrolysis occurs. When solid and liquid-**crystalline** lipid phases coexist, a limited hydrolysis of phosphatidylglycerol can be observed. The results demonstrate the disposition of phosphatidylglycerol in three different pools in the membrane of A. laidlawii. Phospholipase A2 has been used to discriminate between these pools and to estimate the amount of phosphatidylglycerol which is present in the liquid-**crystalline** phase. The present data, however, do not allow a definite localization of the phosphatidylglycerol pools.

L37 ANSWER 21 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1985:329694 BIOSIS
DOCUMENT NUMBER: BA79:109690
TITLE: ACTION OF COBRA VENOM PHOSPHOLIPASE A-2 **EC-3.1.1.4** ON LARGE UNILAMELLAR VESICLES COMPARISON WITH SMALL UNILAMELLAR VESICLES AND MULTIBILAYERS.
AUTHOR(S): KENSIL C R; DENNIS E A
CORPORATE SOURCE: DEP. CHEMISTRY, UNIV. CALIF. AT SAN DIEGO, LA JOLLA, CA 92093.
SOURCE: LIPIDS, (1985) 20 (2), 80-83.
CODEN: LPDSAP. ISSN: 0024-4201.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB Phospholipase A2 (Naja naja naja) catalyzes the hydrolysis of dipalmitoyl phosphatidylcholine in small unilamellar vesicles (SUV) with a faster initial rate than in large unilamellar vesicles (LUV) and multilamellar vesicles (MLV). For the SUV the hydrolysis was initially faster for gel phase than liquid **crystalline** phase phospholipid. For both LUV and MLV, hydrolysis was low except in a small temperature range around the thermotropic phase transition of the phospholipid. In this temperature range, the reaction time course of phospholipase action of dipalmitoyl phosphatidylcholine in LUV and MLV included a lag period. With SUV a lag period also was observed above the phase transition temperature, but it was not observed below it.

L37 ANSWER 22 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1982:171471 BIOSIS
DOCUMENT NUMBER: BA73:31455
TITLE: LIPID PHASE SEPARATION MEDIATES BINDING OF PORCINE PANCREATIC PHOSPHO LIPASE A-2 **EC-3.1.1.4** TO ITS SUBSTRATE.
AUTHOR(S): GOORMAGHTIGH E; VAN CAMPENHOUD M; RUYSSCHAERT J-M
CORPORATE SOURCE: LAB. DE CHIMIE PHYSIQUE DES MACROMOLECULES AUX INTERFACES, UNIV. LIBRE DE BRUXELLES, B-1050 C.P. 206/2 BRUXELLES, BELGIUM.
SOURCE: BIOCHEM BIOPHYS RES COMMUN, (1981) 101 (4), 1410-1418.
CODEN: BBRCA9. ISSN: 0006-291X.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB Multilamellar liposomes made of equimolar mixtures of dimyristoyl and distearoylphosphatidylcholine were hydrolyzed by porcine pancreatic phospholipase A2. Ph-stat titration, equilibrium gel filtration and differential scanning calorimetry were used to study, respectively, the enzymic hydrolysis, the enzyme binding and the lipid phase repartition. The optimal enzyme activity observed in the region where liquid **crystalline** and gel lipid phases coexist, is due to a drastic increase of the enzyme binding to its substrate. Apparently, the border region separating the lipid phases could be a privileged site for enzyme insertion. Increase of lateral compressibility due to coexistence of solid and fluid lipid phases will promote the penetration of the hydrophobic interface recognition site (IRS) of phospholipase A2 into the lipid matrix whereas the active site, distinct from the IRS will attack its substrate independently of the lipid physical state.

L37 ANSWER 23 OF 73 MEDLINE
ACCESSION NUMBER: 1999296614 MEDLINE
DOCUMENT NUMBER: 99296614 PubMed ID: 10366595
TITLE: Role of phosphorylation sites and the C2 domain in regulation of **cytosolic phospholipase A2**.
AUTHOR: Gijon M A; Spencer D M; Kaiser A L; Leslie C C
CORPORATE SOURCE: Division of Basic Science, Department of Pediatrics, National Jewish Medical and Research Center, Denver, Colorado 80206, USA.
CONTRACT NUMBER: HL34303 (NHLBI)
HL61378 (NHLBI)
SOURCE: JOURNAL OF CELL BIOLOGY, (1999 Jun 14) 145 (6) 1219-32.
Journal code: HMV; 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990727
Last Updated on STN: 19990727
Entered Medline: 19990712

AB **Cytosolic phospholipase A2** (**cPLA2**) mediates agonist-induced arachidonic acid release, the first step in eicosanoid production. **cPLA2** is regulated by phosphorylation and by calcium, which binds to a C2 domain and induces its translocation to membrane. The functional roles of phosphorylation sites and the C2 domain of **cPLA2** were investigated. In Sf9 insect cells expressing **cPLA2**, okadaic acid, and the calcium-mobilizing agonists A23187 and CryIC toxin induce arachidonic acid release and translocation of green fluorescent protein (GFP)-**cPLA2** to the nuclear envelope. **cPLA2** is phosphorylated on multiple sites in Sf9 cells; however, only S505 phosphorylation partially contributes to **cPLA2** activation. Although okadaic acid does not increase calcium, mutating the calcium-binding residues D43 and D93 prevents arachidonic acid release and translocation of **cPLA2**, demonstrating the requirement for a functional C2 domain. However, the D93N mutant is fully functional with A23187, whereas the D43N mutant is nearly inactive. The C2 domain of **cPLA2** linked to GFP translocates to the nuclear envelope with calcium-mobilizing agonists but not with okadaic acid. Consequently, the C2 domain is necessary and sufficient for translocation of **cPLA2** to the nuclear envelope when calcium is increased; however, it is required but not sufficient with okadaic acid.

L37 ANSWER 24 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 96:698998 SCISEARCH
THE GENUINE ARTICLE: VJ442
TITLE: NATIVE PEPTIDE INHIBITION - SPECIFIC-INHIBITION OF TYPE-II PHOSPHOLIPASES A(2) BY SYNTHETIC PEPTIDES DERIVED FROM THE PRIMARY SEQUENCE
AUTHOR: TSENG A; INGLIS A S; SCOTT K F (Reprint)
CORPORATE SOURCE: ST VINCENTS HOSP, UNIV NEW S WALES, DEPT MED, LEVEL 9, GARVAN INST BLDG, DARLINGHURST, NSW 2010, AUSTRALIA (Reprint); ST VINCENTS HOSP, UNIV NEW S WALES, DEPT MED, DARLINGHURST, NSW 2010, AUSTRALIA; ST VINCENTS HOSP, UNIV NEW S WALES, GARVAN INST MED RES, DARLINGHURST, NSW 2010,

AUSTRALIA
COUNTRY OF AUTHOR: AUSTRALIA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (27 SEP 1996) Vol. 271, No. 39, pp. 23992-23998.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 38

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The binding of low molecular weight type II phospholipase A(2) (**EC 3.1.1.4**) to membrane surfaces and hydrolysis of phospholipid are thought to involve the formation of a hydrophobic channel into which a single substrate molecule diffuses before cleavage, The floor and right side of the channel are provided by hydrophobic residues 2, 5, and 9 of an amphipathic amino-terminal helix, The channel is postulated to form via a conformational change in this helix and inward movement of a hydrophobic flap (residue 69 side chain). We show that the amino-terminal tryptic peptide of human type II phospholipase A(2) forms a noncovalent complex with the tryptic peptide from residues 70-74 of the enzyme, Further, the 70-74-peptide sequence (FLSYK) dose-dependently inhibits phospholipid hydrolysis in a mixed micelle assay. This native peptide inhibition also occurred with type II enzymes from Crotalus durissus and Crotalus atrox, which have different amino acid sequences at the amino terminus as well as different 70-74 regions of the molecules. Despite significant conservation of tertiary structure among the enzymes, inhibition by each peptide is specific to the enzyme from which the peptide sequence is derived, We propose that these native peptides inhibit enzyme activity via a sequence-specific, noncovalent interaction with the amino-terminal residues of the enzyme, thereby preventing the conformational change on binding to the micelle interface, These experiments demonstrate a new method for specific inhibition of phospholipase A(2) which, in principle, would be applicable to other biologically active polypeptides and proteins.

L37 ANSWER 25 OF 73 MEDLINE
ACCESSION NUMBER: 84108354 MEDLINE
DOCUMENT NUMBER: 84108354 PubMed ID: 6662109
TITLE: Conformational properties of phospholipases A2. Secondary-structure prediction, circular dichroism and relative interface hydrophobicity.
AUTHOR: Dufton M J; Eaker D; Hider R C
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1983 Dec 15) 137 (3) 537-44.
Journal code: EMZ; 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198403
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19900319
Entered Medline: 19840301

AB The sequences of 32 phospholipases A2 (**EC 3.1.1.4**) were analysed by secondary-structure prediction and the results were compared with the available **crystallographic** data. Good agreement is evident between prediction and experiment, especially for helical structure. Circular dichroic spectra were also determined for six enzymes from Elapid snake venom and these, in association with previously published spectra, confirm the main implication of the predictions, namely that all the homologues have qualitatively similar tertiary structures. Consideration was then given to possible structure/activity relationships in the light of the above findings. The relative hydrophobicity/hydrophilicity of the area of the enzyme thought to interact with lipid/water interfaces was predicted and certain correlations were noted with relative penetrating power, species of origin and the presence of beta-neurotoxic properties.

L37 ANSWER 26 OF 73 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998347417 EMBASE

TITLE: Membrane penetration of **cytosolic phospholipase A2** is necessary for its interfacial catalysis and arachidonate specificity.
AUTHOR: Lichtenbergova L.; Yoon E.T.; Cho W.
CORPORATE SOURCE: W. Cho, Department of Chemistry (M/C 111), University of Illinois, 845 West Taylor Street, Chicago, IL 60607-7061, United States. wcho@uic.edu
SOURCE: Biochemistry, (6 Oct 1998) 37/40 (14128-14136).
Refs: 65
ISSN: 0006-2960 CODEN: BICHAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB To determine the mechanism of calcium-dependent membrane binding of **cytosolic phospholipase A2** (**cPLA2**), we measured the interactions of **cPLA2** with phospholipid monolayers and polymerizable mixed liposomes containing various phospholipids. In the presence of calcium, **cPLA2** showed much higher penetrating power than secretory human pancreatic PLA2 toward anionic and electrically neutral phospholipid monolayers. **cPLA2** also showed ca. 30-fold higher binding affinity for nonpolymerized 2,3-bis[12- (lipoyloxy)dodecanoyl]-sn-glycero-1-phosphoglycerol (D-BLPG) liposomes than for polymerized ones where the membrane penetration of protein is significantly restricted. Consistent with this difference in membrane binding affinity, **cPLA2** showed 20-fold higher activity toward fluorogenic substrates, 1-O-(1-pyrenedecyl)-2-arachidonoyl-sn-glycero-3-phosphocholine, inserted in nonpolymerized D-BLPG liposomes than the same substrate in polymerized D-BLPG liposomes. Furthermore, **cPLA2** showed much higher sn-2 acyl group specificity (arachidonate specificity) and headgroup specificity in nonpolymerized D-BLPG liposomes than in polymerized D-BLPG liposomes. Finally, diacylglycerols, such as 1,2-dioleoylsn-glycerol, selectively enhanced the membrane penetration, hydrophobic membrane binding, and interfacial enzyme activity of **cPLA2**. Taken together, these results indicate the following: (1) calcium not only brings **cPLA2** to the membrane surface but also induces its membrane penetration. (2) This unique calcium-dependent membrane penetration of **cPLA2** is necessary for its interfacial binding and substrate specificity. (3) Diacylglycerols might work as a cellular activator of **cPLA2** by enhancing its membrane penetration and hydrophobic membrane binding.

L37 ANSWER 27 OF 73 MEDLINE
ACCESSION NUMBER: 78212489 MEDLINE
DOCUMENT NUMBER: 78212489 PubMed ID: 580900
TITLE: Kinetics of hydrolysis of dispersions of saturated phosphatidylcholines by Crotalus atrox phospholipase A2.
AUTHOR: Tinker D O; Purdon A D; Wei J; Mason E
SOURCE: CANADIAN JOURNAL OF BIOCHEMISTRY, (1978 Jun) 56 (6) 552-8.
Journal code: CHN; 0421034. ISSN: 0008-4018.
PUB. COUNTRY: Canada
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197809
ENTRY DATE: Entered STN: 19900314
Last Updated on STN: 19970203
Entered Medline: 19780925

AB Dispersions of lamellar phase dipalmitoyl phosphatidylcholine (DDPC) and dimyristoyl phosphatidylcholine (DMPC) in 0.01 M CaCl2 were subjected to hydrolysis by phospholipase A2 (**EC 3.1.1.4**) from Crotalus atrox venom. The reaction was followed continuously by titrating the released fatty acids. For hydrolysis of gel phase phosphatides, the steady-state initial velocities were hyperbolic functions of bulk lipid concentrations. At the 'pre-transition' temperature (34 degrees C for DPPC, 15 degrees C for DMPC), there was a large increase in the Michaelis parameter Vmax but no change in the parameter Km. A model was devised to account for these observations, in which the enzyme desorbs from the lipid surface after hydrolysis. The desorption rate constant is postulated to increase above

the pretransition temperature. For hydrolysis of liquid **crystalline** phosphatides, the reaction consisted of a short initial burst of hydrolysis, a long 'lag' period of very slow reaction, followed by a dramatic increase in the reaction rate. Addition of 10 mol% lysolecithin or fatty acid abolished the 'lag' period. It was postulated that the enzyme adsorbs irreversibly to the surface of the liquid **crystalline** phase. Reaction products are postulated to stimulate desorption of enzyme from the surface. Thus, temperature-dependent changes in the rate of hydrolysis of dispersed phosphatidylcholines are attributed to changes in the rate of desorption of the enzyme from the lipid surface.

L37 ANSWER 28 OF 73 MEDLINE
ACCESSION NUMBER: 86000875 MEDLINE
DOCUMENT NUMBER: 86000875 PubMed ID: 4041563
TITLE: Hydrolysis of phosphatidylcholine liposomes by lysosomal phospholipase A is maximal at the phase transition temperature of the lipid substrate.
AUTHOR: Vandenbranden M; De Gand G; Brasseur R; Defrise-Quertain F; Ruysschaert J M
SOURCE: BIOSCIENCE REPORTS, (1985 Jun) 5 (6) 477-82.
Journal code: A6D; 8102797. ISSN: 0144-8463.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198511
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19851112

AB We have measured the rate of hydrolysis of liposomes made of DL-alpha-dipalmitoylphosphatidylcholine (DPPC) and L-alpha-dimyristoylphosphatidylcholine by a soluble fraction of highly purified lysosomes isolated from rat liver. Phospholipids are hydrolyzed into lysophospholipids and fatty acids at a rate which is maximal near the temperature characteristic of the gel to liquid **crystalline** phase transition of the lipid bilayer. This strong influence of the physical properties of the substrate on the enzyme activity suggests a structural analogy between the lysosomal phospholipases of the A type (EC 3.1.1.32 and **EC 3.1.1.4**) and the pancreatic phospholipase A2.

L37 ANSWER 29 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:241776 BIOSIS
DOCUMENT NUMBER: PREV199900241776
TITLE: Purification, **crystallization** and preliminary **X-ray crystallographic** analysis of a phospholipase A2 from Daboia russelli pulchella.
AUTHOR(S): Chandra, Vikas; Nagpal, Akanksha; Srinivasan, A.; Singh, T. P. (1)
CORPORATE SOURCE: (1) Department of Biophysics, All India Institute of Medical Sciences, New Delhi, 110029 India
SOURCE: Acta Crystallographica Section D Biological Crystallography, (April, 1999) Vol. 55, No. 4, pp. 925-926. ISSN: 0907-4449.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Phospholipases are esterolytic enzymes which hydrolyze glycerophospholipids. The pharmacological efficiency of phospholipase A2 (PLA2) enzymes is reflected by their specificity towards a tissue or organ. The Russell's viper has been classified into two classes. Class 1 contains Viper russelli russelli, Viper russelli siamensis and Viper russelli formosensis, whereas class 2 contains Daboia russelli pulchella. The sequence identity between the PLA2s from these two classes is 47%. The novel PLA2 from Daboia russelli pulchella has been **crystallized** using the hanging-drop vapour-diffusion method with ammonium sulfate as precipitating agent. **Crystals** belong to the orthorhombic space group C2221 with unit-cell parameters a = 77.01, b = 92.29, c = 76.90 ANG and two molecules in the asymmetric unit. These **crystals** diffract to about 2.49 ANG resolution using a rotating-anode source.

L37 ANSWER 30 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:448322 BIOSIS
DOCUMENT NUMBER: PREV199497461322
TITLE: **X-ray crystal** structure and molecular dynamics simulation of bovine pancreas phospholipase A-2-n-dodecylphosphorylcholine complex.
AUTHOR(S): Tomoo, Koji; Ohishi, Hirofumi; Ishida, Toshimasa (1); Inoue, Masatoshi; Ikeda, Kiyoshi; Sumiya, Shigeyuki; Kitamura, Kunihiro
CORPORATE SOURCE: (1) Dep. Physical Chem., Osaka Univ. Pharm. Sci., 2-10-65 Kawai, Matsubara, Osaka 580 Japan
SOURCE: Proteins Structure Function and Genetics, (1994) Vol. 19, No. 4, pp. 330-339.
ISSN: 0887-3585.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The **crystal** structure of n-dodecylphosphorylcholine (n-C-12PC)-bovine pancreas phospholipase A-2 (PLA-2) complex provided the following structural characteristics: (1) the dodecyl chain of n-C-12PC was located at the PLA-2 N-terminal helical region by hydrophobic interactions, which corresponds to the binding pocket of 2-acyl fatty acid chain (beta chain) of the substrate phospholipid, (2) the region from Lys-53 to Lys-56 creates a choline-receiving pocket of n-C-12PC and (3) the N-terminal group of Ala-1 shifts significantly toward the Tyr-52 OH group by the binding of the n-C-12PC inhibitor. Since the accuracy of the **X-ray** analysis (R = 0.275 at 2.3 ANG resolution) was insufficient to establish these important **X-ray** insights, the complex structure was further investigated through the molecular dynamics (MD) simulation, assuming a system in aqueous solution at 310K. The MD simulation covering 176 ps showed that the structural characteristics observed by **X-ray** analysis are intrinsic and also stable in the dynamic state. Furthermore, the MD simulation made clear that the PLA, binding pocket is large enough to permit the conformational fluctuation of the n-C-12PC hydrocarbon chain.

L37 ANSWER 31 OF 73 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:162461 CAPLUS
DOCUMENT NUMBER: 124:314202
TITLE: Molecular characterization of seizure-related genes isolated by differential screening
AUTHOR(S): Kajiwara, Kagemasa; Nagawawa, Hideko; Shimizu-Nishikawa, Keiko; Ookura, Tamiko; Kimura, Minoru; Sugaya, Eiichi
CORPORATE SOURCE: Dep. Physiology, Kanagawa Dental College, Yokosuka, 238, Japan
SOURCE: Biochem. Biophys. Res. Commun. (1996), 219(3), 795-99.
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To isolate seizure-related genes, the authors applied differential screening technique to the cDNA library which was constructed from primary cultured cerebral cortical cells treated with pentylenetetrazol (PTZ). Northern blotting anal. of mRNA levels in the cerebra after systemic administration of PTZ confirmed the results of differential screening procedure: 6 clones showed increased mRNA level and 3 clones showed decreased expression with PTZ. Interestingly, 4 genes which were isolated by this technique were related to intracellular calcium action. They were **cytosolic phospholipase A2**, 78 kDa glucose regulated protein, SEZ-15 which has an EF hand motif and PTZ-17 that causes calcium current in Xenopus oocyte with PTZ application. These data and the authors' previous results suggest that intracellular calcium may play an important role for seizure-related pathophysiol. changes in neuronal cells.

L37 ANSWER 32 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:3348 BIOSIS
DOCUMENT NUMBER: PREV199395003348
TITLE: Interaction mode of n-dodecylphosphorylcholine, a substrate analogue, with bovine pancreas phospholipase A-2 as determined by **X-ray crystal** analysis.

AUTHOR(S): Tomoo, Koji; Ohishi, Hirofumi; Doi, Mitsunobu; Ishida, Toshimasa (1); Inoue, Masatoshi; Ikeda, Kiyoshi; Mizuno, Hiroshi
CORPORATE SOURCE: (1) Dep. Physical Chemistry, Osaka University Pharmaceutical Sciences, 2-10-65 Kawai, Matsubara, Osaka 580 Japan
SOURCE: Biochemical and Biophysical Research Communications, (1992) Vol. 187, No. 2, pp. 821-827.
ISSN: 0006-291X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Three-dimensional structure of a bovine pancreas phospholipase A-2 (PLA-2) **crystal** complexed with n-dodecylphosphorylcholine (n-C-12PC), a substrate-type inhibitor, has been determined by the **X-ray** diffraction method. The present conventional R value is 0.275 at 2.4 ANG resolution. The binding node of n-C-12PC to the PLA-2 was clearly indicated, where the dodecyl chain was stably held by the hydrophobic contacts with the N-terminal rigion of PLA-2 (Leu-2, Phe-5, and Ile-9), and the choline moiety was contacted with the hydrophobic space created by the side chains of Lys-53 and 56. The present result indicates that remarkable changes from the native PLA-2 structure are caused at the N-terminal and middle (residues 60 to 70) regions by the binding of n-C-12PC to the enzyme.

L37 ANSWER 33 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:507087 BIOSIS
DOCUMENT NUMBER: PREV199699229443
TITLE: High-resolution **X-ray crystallography** reveals precise binding interactions between human nonpancreatic secreted phospholipase A-2 and a highly potent inhibitor (FPL67047XX.
AUTHOR(S): Cha, Sun-Shin; Lee, Dennis; Adams, Jerry; Kurdyla, Jeffrey T.; Jones, Christopher S.; Marshall, Lisa A.; Bolognese, Brian; Abdel-Meguid, Sherin S.; Oh, Byung-Ha (1)
CORPORATE SOURCE: (1) Dep. Life Sci., Pohang Univ. Sci. Technol., Pohang, Kyungbuk 790-784 South Korea
SOURCE: Journal of Medicinal Chemistry, (1996) Vol. 39, No. 20, pp. 3878-3881.
ISSN: 0022-2623.
DOCUMENT TYPE: Article
LANGUAGE: English

L37 ANSWER 34 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:349371 BIOSIS
DOCUMENT NUMBER: PREV199396046371
TITLE: **Crystallization** and preliminary **X-ray** study of Agkistrodon halys blomhoffii phospholipase A-2 complexed with a specific inhibitor.
AUTHOR(S): Tomoo, Koji; Fujii, Shinobu; Ishida, Toshimasa (1); Inoue, Masatoshi; Ikeda, Kiyoshi; Samejima, Yuji; Iwama, Seiji; Katsumura, Shigeo
CORPORATE SOURCE: (1) Dep. Physical Chemistry, Osaka Univ. Pharmaceutical Sciences, 2-10-65 Kawai, Matsubara, Osaka 580 Japan
SOURCE: Journal of Biochemistry (Tokyo), (1993) Vol. 113, No. 4, pp. 411-412.
ISSN: 0021-924X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Phospholipase A-2 from the venom of Agkistrodon halys blomhoffii has been **crystallized** as a complex with a specific inhibitor, (S)-2-dodecanoyl-amino-3-hexanol-1-phosphoglycol. The complex **crystals** belong to the hexagonal space group, P6-122 (or P6-522), with cell dimensions of a = b = 61.13 ANG , and c = 173.15 ANG . The diffraction extends to at least 2.3 ANG resolution.

L37 ANSWER 35 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:255383 BIOSIS
DOCUMENT NUMBER: PREV199800255383
TITLE: **Crystallization** and preliminary Xx-ray diffraction analysis of a LYS49-PLA2 homologue from

Cerrophidion godmani venom.
AUTHOR(S): de Azevedo, W. F., Jr.; Ward, R. J.; Gutierrez, J. M.; Diaz-Oreiro, C.; Arni, R. K. (1)
CORPORATE SOURCE: (1) Dep. Physics, IBILCE/UNESP, Sao Jose do Rio Pretro-SP CP 136, CEP 150540000 Brazil
SOURCE: Protein and Peptide Letters, (April, 1998) Vol. 5, No. 2, pp. 121-126.
ISSN: 0929-8665.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Lys49-Phospholipase A2 (Lys49-PLA2) homologues damage membranes by a Ca2+-independent mechanism which does not involve catalytic activity. The myotoxic Lys-49 phospholipase myotoxin II from Cerrophidion (Bothrops) godmani has been **crystallized**, and **X-ray** diffraction data were collected to 2.8 ANG resolution. Preliminary analysis reveals the presence of one molecule in the asymmetric unit.

L37 ANSWER 36 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:130594 BIOSIS
DOCUMENT NUMBER: PREV199799422407
TITLE: High specificity of human secretory class II phospholipase A-2 for phosphatidic acid.
AUTHOR(S): Snitko, Yana; Yoon, Edward T.; Cho, Wonhwa (1)
CORPORATE SOURCE: (1) Dep. Chem., Univ. Illinois at Chicago, 845 West Taylor St., Chicago, IL 60607-7061 USA
SOURCE: Biochemical Journal, (1997) Vol. 321, No. 3, pp. 737-741.
ISSN: 0264-6021.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Lysophosphatidic acid (LPA) is a potent lipid second messenger which stimulates platelet aggregation, cell proliferation and smooth-muscle contraction. The phospholipase A-2 (PLA-2)-catalysed hydrolysis of phosphatidic acid (PA) is thought to be a primary synthetic route for LPA. Of the multiple forms of PLA-2 present in human tissues, human secretory class-II PLA-2 (hsPLA-2) has been implicated in the production of LPA from platelets and whole blood cells challenged with inflammatory stimuli. To explore further the possibility that hs-PLA-2 is involved in the production of LPA, we rigorously measured the phospholipid head group specificity of hs-PLA-2 by a novel PLA-2 kinetic system using polymerized mixed liposomes. Kinetic analysis of recombinant hs-PLA-2 demonstrates that hs-PLA-2 strongly prefers PA as substrate over other phospholipids found in the mammalian plasma membrane including phosphatidylserine (PS), phosphatidylcholine (PC) and phosphatidylethanolamine (PE). The order of preference is PA mchgt PE apprxeq PS gt PC. To identify amino acid residues of hs-PLA, that are involved in its unique substrate specificity, we mutated two residues, Glu-56 and Lys-69, which were shown to interact with the phospholipid head group in the **X-ray-crystallographic** structure of the hs-PLA-2-transition-state-analogue complex. The K69Y mutant showed selective inactivation toward PA whereas the E56K mutant displayed a most pronounced inactivation to PE. Thus it appears that Lys-69 is at least partially involved in the PA specificity of hs-PLA-2 and Glu-56 in the distinction between PE and PC. In conjunction with a recent cell study (Fourcade, Simon, Viode, Rugani, Leballe, Ragab, Fournie, Sarda and Chap (1995) Cell 80, 919-927), these studies suggest that hs-PLA-2 can rapidly hydrolyse PA molecules exposed to the outer layer of cell-derived microvesicles and thereby produce LPA.

L37 ANSWER 37 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:210109 BIOSIS
DOCUMENT NUMBER: PREV199497223109
TITLE: Sequence analysis and expression of phospholipase A-2 from Taiwan cobra.
AUTHOR(S): Pan, Fu-Ming; Yeh, Maw-Sheng; Chang, Wen-Chang; Hung, Chin-Chun; Chiou, Shyh-Horng (1)
CORPORATE SOURCE: (1) Inst. Biochem. Sci., Natl. Taiwan Univ., P.O. Box 23-106, Academia Sinica, Taipei 10098 Taiwan
SOURCE: Biochemical and Biophysical Research Communications, (1994) Vol. 199, No. 2, pp. 969-976.
ISSN: 0006-291X.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Polymerase chain reaction (PCR) was employed to amplify cDNAs constructed from the poly(A)+RNA of venom glands in Taiwan cobras to facilitate the cloning and sequencing of phospholipase A-2 (PLA-2) gene. The PCR product was then subcloned into pUC18 vector and transformed in E. coli strain JM109. Plasmids purified from the positive clones were prepared for nucleotide sequencing by dideoxynucleotide chain-termination method. Sequencing several clones containing about 0.5 kb DNA inserts constructed a complete and unambiguous full-length reading frame of 468 base pairs covering a precursor for phospholipase A-2 with a deduced mature protein sequence of 119 amino acids and a 27 amino-acid segment of signal peptide. The sequenced major PLA-2 with pI 4.991 shows a high degree of sequence homology to those PLA-2 of the same or closely-related genus. The deduced protein sequence allows us to correct and resolve some discrepancy between the sequences determined by conventional protein sequencing (Toxicon, 19, 141(1981)) and **X-ray crystallography** (Science, 250, 1560(1990)). Expression of PLA-2 in E. coli vector generated a polypeptide which can cross-react with the antiserum against the native and purified PLA-2 from the same cobra venom albeit with a much lower activity.

L37 ANSWER 38 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1995:297247 BIOSIS
DOCUMENT NUMBER: PREV199598311547
TITLE: **Crystal** structure analysis of phospholipase A-2 from Trimeresurus flavoviridis (Habu snake) venom at 1.5 A resolution.
AUTHOR(S): Suzuki, Atsuo (1); Matsueda, Eiichiro; Yamane, Takashi; Ashida, Tamaichi; Kihara, Hiroshi; Ohno, Motonori
CORPORATE SOURCE: (1) Dep. Biotechnol., Sch. Eng., Nagoya Univ., Furo-cho, Chikusa-ku, Nagoya, Aichi 464-01 Japan
SOURCE: Journal of Biochemistry (Tokyo), (1995) Vol. 117, No. 4, pp. 730-740.
ISSN: 0021-924X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The **crystal** structure of dimeric phospholipase A-2 (PLA-2) from the venom of Hahn snake, Trimeresurus flavoviridis, has been determined by the molecular replacement method, and has been refined at 1.5 ANG resolution to an R-factor of 0.175. In the **crystal**, T. flavoviridis PLA-2 forms a dimer using two 14 kDa subunits related by a pseudo 2-fold axis. Along the axis, the dimer has a narrow channel passing through it. Although no calcium ion is present in the calcium binding site, the peptide-chain folding of the subunits, the conformation of the catalytic residues, and the hydrogen-bonding network around the active sites are almost identical to those of the group I/II monomeric or dimeric PLA-2s. The catalytic residues in both subunits are buried in the interior of the dimer and are inaccessible to substrate from the bulk solvent. In addition, the subunits of the dimer interact with each other at the hydrophobic region of the molecular surface where the entrance to the active site opens and where PLA-2 is presumed to interact with the phospholipid of the substrate. Therefore, it is inferred that dimerization of T. flavoviridis PLA-2 is the result of free-energy minimization by excluding the hydrophobic molecular surface from the aqueous solvent, rather than being required for the enzymatic function.

L37 ANSWER 39 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:296618 BIOSIS
DOCUMENT NUMBER: PREV199396014843
TITLE: Arginine-53 is involved in head-group specificity of the active site of porcine pancreatic phospholipase A-2.
AUTHOR(S): Lugtigheid, Richard B.; Otten-Kuipers, Maaike A.; Verheij, Hubertus M. (1); De Haas, Geard H.
CORPORATE SOURCE: (1) Dep. Enzymology Protein Engineering, University Utrecht, CBLE, P.O. Box 80.065, NL-3508 TB Utrecht, The Netherlands
SOURCE: European Journal of Biochemistry, (1993) Vol. 213, No. 1, pp. 517-522.
ISSN: 0014-2956.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The **X-ray** structure of a mutant porcine pancreatic

phospholipase A-2 inhibitor complex (Thunnissen et al. (1990) Nature 347, 689-691) has been determined. This structure shows several interactions between the sn-2-acyl chain and the phosphate moiety of the inhibitor at sn-3 and the protein. The interactions of the remaining part of the polar head group are less clear. Because Arg53 is in close proximity to the head group, we tested the importance of charge at position 53 on enzymatic activity and specificity. Arg53 has been replaced by a glutamine and a glutamic acid in mutants R53Q and R53E, respectively. The effects of the mutations were tested with both zwitterionic and anionic substrates. With monomeric, zwitterionic, (R,S)-1,2-dihexanoyldithiopropyl-3-phosphocholine as substrate, the mutants R53Q and R53E display twofold and sevenfold, respectively, increased k-cat/K-m values, composed of increased k-cat and decreased K-m values. Tested on micelles of zwitterionic (R)-1,2-dioctanoylglycero-3-phosphocholine the mutants R53Q and R53E are more active than the native enzyme, whereas these mutations have an opposite effect on the activity on anionic (R)-1,2-dioctanoylglycero-3-phosphoglycol. Thus, whereas the native enzyme is 0.3 times as active on zwitterionic as on the anionic substrate, these ratios are 1.0 (R53Q) and 1.7 (R53E) for the mutants. No changes in activity were observed with the anionic substrate (R)-1,2-dioctanoylglycero-3-sulfate. Binding studies with substrate-derived inhibitors confirmed the increased affinity for zwitterionic phospholipids and the reduced affinity for anionic phospholipids. The kinetic and binding data indicate the involvement of the charge of residue 53 in head-group specificity and suggest a position of residue 53 closer to the choline or glycol than to the phosphate.

L37 ANSWER 40 OF 73 LIFESCI COPYRIGHT 2001 CSA
ACCESSION NUMBER: 88:46527 LIFESCI
TITLE: Inhibition of phospholipase A sub(2) by some long chain alkylamines.
AUTHOR: Davis, P.D.; Nixon, J.S.; Wilkinson, S.E.; Russell, M.G.N.
CORPORATE SOURCE: Roche Prod. Ltd., P.O. Box 8, Welwyn Garden City, Hertfordshire AL7 3AY, UK
SOURCE: TRANS. BIOCHEM. SOC., (1988) vol. 16, no. 5, pp. 816-817.
DOCUMENT TYPE: Journal
FILE SEGMENT: L
LANGUAGE: English
AB Phospholipase A sub(2) (PLA sub(2); **EC 3.1.1.4**) releases arachidonic acid from phospholipids in the rate-limiting step of eicosanoid generation. Since eicosanoids are implicated in inflammatory processes, inhibition of this pathway may be therapeutically beneficial. The authors have synthesized a series of inhibitors designed by study of the **X-ray crystal** structure of bovine pancreatic PLA sub(2). Reveals a large hydrophobic cavity containing only two easily accessible, polar amino acid side-chains: those of His-48 and Asp-49. These residues are involved in the hydrolysis mechanism and calcium binding, respectively.

L37 ANSWER 41 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:224879 BIOSIS
DOCUMENT NUMBER: PREV199799516595
TITLE: **Crystal** structure determination of basic phospholipase A-2 from venom of Agkistrodon halys pallas by molecular replacement method.
AUTHOR(S): Meng Wuyi, Lin Zhengjiong (1); Zhou Yuancong
CORPORATE SOURCE: (1) State Key Lab. Biomacromolecules, Inst. Biophysics, Chinese Acad. Sci., Beijing 100101 China
SOURCE: Science in China Series C Life Sciences, (1996) Vol. 39, No. 6, pp. 584-591.
ISSN: 1006-9305.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Basic phospholipase A-2 (BPLA-2) from the venom of Agkistrodon halys pallas has a strong ability to hemolyze erythrocytes. The asymmetrical unit of P2-12-12-1 crystal of **BPLA**-2 contains two molecules. Self-rotation function was used to study the orientation relationship of these two molecules. Cross-rotation and translation functions were then used to determine the orientations and positions of the two molecules in the unit cell. The model building and preliminary structure refinement were carried out. The result shows that the two molecules in the asymmetrical unit of orthorhombic crystal are **related** by a

non-crystallographic 2-**fold** symmetry axis.

L37 ANSWER 42 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:102078 BIOSIS
DOCUMENT NUMBER: PREV199698674213
TITLE: **Crystal** structure of an acidic phospholipase A-2 from the venom of Agkistrodon halys pallas at 2.0 A resolution.
AUTHOR(S): Wang, Xiao-Qiang; Yang, Jian; Gui, Lu-Lu; Lin, Zheng-Jiong (1); Chen, Yuan-Cong; Zhou, Yuan-Cong
CORPORATE SOURCE: (1) National Lab. Biomacromolecules, Inst. Biophysics Academia Sinica, Beijing 100101 China
SOURCE: Journal of Molecular Biology, (1996) Vol. 255, No. 5, pp. 669-676.
ISSN: 0022-2836.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The **crystal** structure of acidic phospholipase A-2 from the venom of Agkistrodon halys pallas has been determined by molecular replacement at 2.0 ANG resolution to a **crystallographic** R-factor of 0.157. The overall structure of the molecule is very similar to those of other phospholipase A-2 species of known structure. The catalytic site, the hydrophobic channel and the N-terminal region show greatest structural conservation. The Ca-2+-binding region has a conformation that resembles closely that of bovine PLA-2 rather than Crotalus atrox PLA-2. Compared with other PLA-2 species, the conformation of the C-terminal ridge shows significant difference due to the insertion of two residues. A unique aromatic patch appears on one face of the molecules, surrounded by two acidic residues, the relevant features of this structure and their possible biological implications are discussed.

L37 ANSWER 43 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:441305 BIOSIS
DOCUMENT NUMBER: PREV199800441305
TITLE: **Crystal** structure of piratoxin-I: A calcium-independent, myotoxic phospholipase A2-homologue from Bothrops pirajai venom.
AUTHOR(S): Azevedo, W. F. De, Jr.; Ward, R. J.; Canduri, F.; Soares, A.; Giglio, J. R.; Arni, R. K. (1)
CORPORATE SOURCE: (1) Dep. Phys., IBILCE/UNESP, CP 136, CEP 15054-000, Sao Jose do Rio Preto - SP Brazil
SOURCE: Toxicon, (Oct., 1998) Vol. 36, No. 10, pp. 1395-1406.
ISSN: 0041-0101.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The **crystal** structure of piratoxin-I (PrTX-I) a Lys49 homologue isolated from the venom of Bothrops pirajai has been determined Tyr28 fwdarw Asn, Gly32 fwdarw Leu and Asp49 fwdarw Lys, result in an altered conformation of this loop. The analysis of the position of the epsilon-amino group of Lys49 in the PrTX-I structure indicates that it fills the site normally occupied by the calcium ion in the catalytically active phospholipases. In contrast to the homologous monomeric Lys49 variant from Agkistrodon piscivorus piscivorus (App), PrTX-I is present as a dimer in the **crystalline** state, as observed in the structures of myotoxin II from Bothrops asper and Bothropstoxin I from Bothrops jararacussu. The two molecules in the asymmetric unit in the **crystal** structure of PrTX-I are related by a nearly perfect two-fold symmetry axis, yet the dimeric structure is radically different from the dimeric structure of the phospholipase from Crotalus atrox. In the C. atrox structure the dimer interface occludes the active sites, whereas in the PrTX-I structure they are exposed to solvent.

L37 ANSWER 44 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:408425 BIOSIS
DOCUMENT NUMBER: PREV199799714628
TITLE: **Crystal** structure of vipoxin at 2.0 A: An example of regulation of a toxic function generated by molecular evolution.
AUTHOR(S): Perbandt, M.; Wilson, J. C.; Eschenburg, S.; Mancheva, I.; Aleksiev, B.; Genov, N.; Willingmann, P.; Weber, W.; Singh, T. P.; Betzel, C. (1)

CORPORATE SOURCE: (1) Inst. Biochem., Free Univ. Berlin, Thielallee 63, 14195 Berlin Germany
SOURCE: FEBS Letters, (1997) Vol. 412, No. 3, pp. 573-577. ISSN: 0014-5793.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Vipoxin is the main toxic component in the venom of the Bulgarian snake Vipera ammodytes meridionalis, the most toxic snake in Europe. Vipoxin is a complex between a toxic phospholipase A-2 (PLA-2) and a non-toxic protein inhibitor. The structure is of genetic interest due to the high degree of sequence homology (62%) between the two functionally different components. The structure shows that the formation of the complex in vipoxin is significantly different to that seen in many known structures of phospholipases and contradicts the assumptions made in earlier studies. The modulation of PLA-2 activity is of great pharmacological interest, and the present structure will be a model for structure-based drug design.

L37 ANSWER 45 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:483095 BIOSIS
DOCUMENT NUMBER: PREV199699198351
TITLE: Phospholipase A-2: A structural review.
AUTHOR(S): Arni, R. K.; Ward, R. J.
CORPORATE SOURCE: Dep. Physics, IBILCE/UNESP, Sao Jose do Rio Preto-SP CP 136, CEP 15054-000 Brazil
SOURCE: Toxicon, (1996) Vol. 34, No. 8, pp. 827-841. ISSN: 0041-0101.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB Phospholipases A-2 (PLA-2) are widely distributed in nature and are well characterized proteins with respect to their catalytic and pharmacological activities. A wealth of structural information has recently become available both from **X-ray** diffraction and NMR studies, and although a detailed model of the catalytic mechanism of PLA-2 has been proposed, the structural bases of other aspects of PLA-2 function, such as interfacial activation and venom PLA-2 pharmacological activities, are still under debate. An appreciation of the PLA-2 protein structure will yield new insights with regard to these activities. The salient structural features of the class I, II and III PLA-2 are discussed with respect to their functional roles.

L37 ANSWER 46 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:326591 BIOSIS
DOCUMENT NUMBER: PREV199800326591
TITLE: Structure of a snake venom phospholipase A2 modified by p-bromo-phenacyl-bromide.
AUTHOR(S): Zhao, Haiyan; Tang, Liang; Wang, Xiaoqiang; Zhou, Yuancong; Lin, Zhengjiong (1)
CORPORATE SOURCE: (1) Natl. Lab. Biomarcromol., Inst. Biophysics, Acad. Sinica, Beijing 100101 China
SOURCE: Toxicon, (June, 1998) Vol. 36, No. 6, pp. 875-886. ISSN: 0041-0101.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The **crystal** structure of acidic phospholipase A2 (APLA2) from Agkistrodon halys pallas covalently modified by p-bromo-phenacyl-bromide (pBPB) was determined to a resolution of 2.0 ANG by an isomorphous difference Fourier method with the native APLA2 structure as an initial model and refined to a **crystallographic** R factor of 15.3%. The modified APLA2 structure is remarkably similar to that of the native one. Least-squares superposition of Calpha atoms of native and modified APLA2 results in a root-mean-square coordinate deviation of 0.243 ANG. The p-bromo-phenacyl group near the active site occupies a position similar to that in pBPB modified bovine pancreatic PLA2. The inhibitor covalently bound to the ND1 atom of His48 fits well in the hydrophobic channel, forming extensive hydrophobic interactions with the surrounding residues, especially with the side chains of Phe5 and Cys45 and the main chain of Gly30. However, the inhibitor does not change the conformation of these residues except that Trp31 at the entrance of the hydrophobic channel moves slightly toward the inhibitor. Compared with native APLA2, the Ca2+-binding loop shows a little conformational change and a cation, probably Na+, occupies in the position of Ca2+. The binding of pBPB to

APLA2 induce no other significant conformational changes in the enzyme molecule elsewhere.

L37 ANSWER 47 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1995:509447 BIOSIS
DOCUMENT NUMBER: PREV199598514497
TITLE: Solution structure of porcine pancreatic phospholipase A2.
AUTHOR(S): Van Den Berg, Bert; Tessari, Marco; De Haas, Gerard H.; Verheij, Hubertus M.; Boelens, Rolf; Kaptein, Robert (1)
CORPORATE SOURCE: (1) Bijvoet Cent. Biomolecular Res., Utrecht Univ., Padualaan 8, 3584 CH Utrecht Netherlands
SOURCE: EMBO (European Molecular Biology Organization) Journal, (1995) Vol. 14, No. 17, pp. 4123-4131. ISSN: 0261-4189.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The lipolytic enzyme phospholipase A-2 (PLA-2) is involved in the degradation of high-molecular weight phospholipid aggregates in vivo. The enzyme has very high catalytic activities on aggregated substrates compared with monomeric substrates, a phenomenon called interfacial activation. **Crystal** structures of PLA-2s in the absence and presence of inhibitors are identical, from which it has been concluded that enzymatic conformational changes do not play a role in the mechanism of interfacial activation. The high-resolution NMR structure of porcine pancreatic PLA-2 free in solution was determined with heteronuclear multi-dimensional NMR methodology using doubly labeled N-labeled protein. The solution structure of PLA-2 shows important deviations from the **crystal** structure. In the NMR structure the A1a1 alpha-amino group is disordered and the hydrogen bonding network involving the N-terminus and the active site is incomplete. The disorder observed for the N-terminal region of PLA-2 in the solution structure could be related to the low activity of the enzyme towards monomeric substrates. The NMR structure of PLA-2 suggests, in contrast to the **crystallographic** work, that conformational changes do play a role in the interfacial activation of this enzyme.

L37 ANSWER 48 OF 73 MEDLINE
ACCESSION NUMBER: 1999196499 MEDLINE
DOCUMENT NUMBER: 99196499 PubMed ID: 10098863
TITLE: A nuclear microscopic study of elemental changes in the rat hippocampus after kainate-induced neuronal injury.
AUTHOR: Ong W Y; Ren M Q; Makjanic J; Lim T M; Watt F
CORPORATE SOURCE: Department of Anatomy, National University of Singapore, Singapore.
SOURCE: JOURNAL OF NEUROCHEMISTRY, (1999 Apr) 72 (4) 1574-9. Journal code: JAV; 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990426
Last Updated on STN: 19990426
Entered Medline: 19990413
AB The effect of intracerebroventricular kainate injection on the elemental composition of the hippocampus was studied in adult Wistar rats, at 1 day and 1, 2, 3, and 4 weeks postinjection, using a nuclear microscope. An increase in calcium concentration was observed on the injected side from 1 day postinjection. The increase peaked at 3 weeks postinjection, reaching a concentration of 18 times normal. Large numbers of glial cells but no neurons were observed in the lesioned CA fields at this time, suggesting that an increased calcium level was present in glial cells. This was confirmed by high-resolution elemental maps of the lesioned areas, which showed very high intracellular calcium concentrations in almost all glial cells. It is possible that the high intracellular calcium level could activate calcium-dependent enzymes, including calpain II and **cytosolic phospholipase A2**, shown to be expressed in reactive glial cells after kainate injections. In addition to calcium, an increase in iron content was also observed at the periphery of the glial scar at 4 weeks postinjection. Because free iron could catalyze the formation of free radicals, the late increase in iron content may be

related to oxygen radical formation during neurodegeneration.

L37 ANSWER 49 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1995:323186 BIOSIS
DOCUMENT NUMBER: PREV199598337486
TITLE: Structure of a calcium-independent phospholipase-like myotoxic protein from Bothrops asper venom.
AUTHOR(S): Arni, R. K. (1); Ward, R. J. (1); Gutierrez, J. M.; Tulinsky, A.
CORPORATE SOURCE: (1) Dep. Physics, UNEXSP-IBILCE, Cx.P. 136, 15054-000 Sao Jose do Rio Preto, SP Brazil
SOURCE: Acta Crystallographica Section D Biological Crystallography, (1995) Vol. 51, No. 3, pp. 311-317. ISSN: 0907-4449.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Myotoxin II, a myotoxic calcium-independent phospholipase-like protein isolated from the venom of Bothrops asper, possesses no detectable phospholipase activity. The **crystal** structure has been determined and refined at 2.8 ANG to an R factor of 16.5% (F gt 3-sigma) with excellent stereochemistry. Amino-acid differences between catalytically active phospholipases and myotoxin II in the Ca-2+-binding region, specifically the substitutions Tyr28 fwdarw Asn, Gly32 fwdarw Leu and Asp49 fwdarw Lys, result in an altered local conformation. The key difference is that the epsilon-amino group of Lys49 fills the site normally occupied by the calcium ion in catalytically active phospholipases. In contrast to the homologous monomeric Lys49 variant from Agkistrodon piscivorus piscivorus, myotoxin II is present as a dimer both in solution and in the **crystalline** state. The two molecules in the asymmetric unit are related by a nearly perfect two-fold axis, yet the dimer is radically different from the dimer formed by the phospholipase from Crotalus atrox. Whereas in C. atrox the dimer interface occludes the active sites, in myotoxin II they are exposed to solvent.

L37 ANSWER 50 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:539827 BIOSIS
DOCUMENT NUMBER: PREV199497552827
TITLE: Effects of specific fatty acid acylation of phospholipase A-2 on its interfacial binding and catalysis.
AUTHOR(S): Shen, Zhen; Wu, Shih-Kwang; Cho, Wonhwa (1)
CORPORATE SOURCE: (1) Dep. Chemistry, Univ. Ill. Chicago, 845 West Taylor Street, Chicago, IL 60607-7061 USA
SOURCE: Biochemistry, (1994) Vol. 33, No. 38, pp. 11598-11607. ISSN: 0006-2960.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Monomeric phospholipase A-2 (PLA-2) from the venom of Agkistrodon piscivorus piscivorus (App-D49) was treated with 3-acyloxy-4-nitrobenzoic acids to acylate the epsilon-amino groups of two lysines (Lys-7 and Lys-10) in the amino terminal region. Resulting 7,10-diacylated-App-D49s, with acyl groups ranging from lauroyl to palmitoyl, spontaneously aggregated in solution. By contrast, 7,10-dioctanoyl-App-D49 existed as a monomer under the same condition. Kinetic and interfacial binding properties of diacylated enzymes indicated that they catalyzed the hydrolysis at the interface as a monomer. When compared to nonacylated App-D49, diacylated enzymes showed slightly increased activity or decreased activity toward monodispersed 1,2-dibutyryl-sn-glycero-3-phosphocholine, Triton X-100/1,2-dilauroyl-sn-glycero-3-phosphocholine mixed micelles, and small unilamellar vesicles (SUV) of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC). Toward densely-packed liquid-**crystalline** phospholipid bilayers, such as large unilamellar vesicles (LUV) of POPC, however, diacylated enzymes exhibited a large increase in activity, which reached up to 250-fold for 7,10-dilauroyl-App-D49 ((k-cat/K-m)app = (1.0 +- 0.02) times 10-6 M-1 s-1). Measurements of the penetration of individual diacylated enzymes into 2-oleoyl-3-palmitoyl-sn-glycero-1-phosphocholine (i.e., D-POPC) monolayers indicated that the acyl groups enhanced the interfacial binding of protein by interacting with hydrocarbon moieties of phospholipids and that these hydrophobic interactions remained effective even when the phospholipid packing density was high. Furthermore, fluorometric measurements of the binding of diacylated enzymes to polymerized vesicles

of 1,2-bis(12(lipoyloxy)dodecanoyl)-sn-glycero-3-phosphocholine showed that the hydrophobic interactions increased the enzymatic activity toward LUV by accelerating the migration of enzyme molecules to vesicle surfaces. The analysis of the kinetic course of POPC LUV hydrolysis showed that diacylated enzymes as a catalyst were superior to nonacylated App-D49 in that they were not only more catalytically efficient but also able to catalyze more turnovers without being trapped in product-containing vesicles. In summary, the acylation of App-D49 by 3-acyloxy-4-nitrobenzoic acids provides a simple and convenient way of converting the enzyme into a highly active form toward densely-packed liquid-**crystalline** phospholipid bilayers, which might have potential industrial and biomedical applications.

L37 ANSWER 51 OF 73 MEDLINE
ACCESSION NUMBER: 95105074 MEDLINE
DOCUMENT NUMBER: 95105074 PubMed ID: 7806430
TITLE: Pentoxifylline inhibits tumor necrosis factor-alpha-mediated cytotoxicity and cytostasis in L929 murine fibrosarcoma cells.
AUTHOR: Takahashi G W; Montgomery R B; Stahl W L; Crittenden C A; Valentine M A; Thorning D R; Andrews D F 3rd; Lilly M B
CORPORATE SOURCE: Medical and Pathology Services, Seattle Veterans Affairs Medical Center, Washington.
CONTRACT NUMBER: CA18029 (NCI)
CA45672 (NCI)
HL31782 (NHLBI)
+
SOURCE: INTERNATIONAL JOURNAL OF IMMUNOPHARMACOLOGY, (1994 Sep) 16 (9) 723-36.
Journal code: GRI; 7904799. ISSN: 0192-0561.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950215
Last Updated on STN: 19970203
Entered Medline: 19950202

AB Tumor necrosis factor-alpha (TNF alpha) is recognized as a principal mediator of a variety of inflammatory conditions. In animal models, pentoxifylline attenuates the morbidity and mortality of bacterial sepsis, an effect which has been attributed to its ability to suppress the induction of TNF alpha. To determine whether pentoxifylline also directly inhibits the effects of TNF alpha, the ability to inhibit cytotoxicity on the TNF alpha-sensitive murine fibrosarcoma cell line, L929, was examined. Cell viability was assessed by **crystal** violet staining and cell proliferation was assessed by [3H]-thymidine uptake assay. TNF alpha induced dose-dependent cytotoxicity. At concentrations of TNF alpha of 1000 U/ml, viability at 3 days was approximately 35% of control. When L929 cells were co-incubated with TNF alpha (1000 U/ml) and pentoxifylline (1 mM), cell viability increased to approximately 75% of control (P = 0.001). At concentrations of TNF alpha of 10,000 U/ml, cell viability which was 11% of control with TNF alpha alone increased to 53% in the presence of pentoxifylline (P = 0.002). TNF alpha at 1000 and 10,000 U/ml concentrations decreased [3H]-thymidine uptake to approximately 5% of control values. Co-incubation with pentoxifylline significantly increased uptake to 13% of control at both TNF alpha concentrations (P = 0.002). Pentoxifylline did not affect the level of type I TNF alpha receptor--ligand cross-link product. However, in TNF alpha receptor binding assays, incubation with pentoxifylline 1 mM for 4 h was associated with an increase in the receptor affinity (control: KD = 0.42 nM vs pentoxifylline-treated: KD = 0.21 nM, P = 0.006), without significant change in number of type I TNF alpha receptors, suggesting that pentoxifylline affects post-receptor signalling events. We have observed that pentoxifylline prevents the TNF alpha-mediated activation of sn-2 arachidonic acid-specific **cytosolic phospholipase A2**, an important component of the signal transduction pathway of TNF alpha cytotoxicity. Because pentoxifylline does not inhibit all activities mediated by the type I TNF alpha receptor, its selective inhibition of post-receptor signalling may facilitate further study into the mechanisms underlying the diverse effects of TNF alpha.

L37 ANSWER 52 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:311479 BIOSIS
DOCUMENT NUMBER: PREV199699033835
TITLE: 1H, 15N and 13C resonance assignments and secondary structure of group II phospholipase A2 from Agkistrodon piscivorus piscivorus: Presence of an amino-terminal helix in solution.
AUTHOR(S): Jerala, Roman; Almeida, Paulo F. F.; Ye, Qiang; Biltonen, Rodney L.; Rule, Gordon S. (1)
CORPORATE SOURCE: (1) Dep. Pharmacol., Univ. Va. Sch. Med., P.O. Box 440, Charlottesville, VA 22908 USA
SOURCE: Journal of Biomolecular NMR, (1996) Vol. 7, No. 2, pp. 107-120.
ISSN: 0925-2738.
DOCUMENT TYPE: Article
LANGUAGE: English
AB 1H, 15N and 13C resonance assignments are presented for the group II phospholipase A2 (PLA2) from Agkistrodon piscivorus piscivorus. The secondary structure of the enzyme has been inferred from an analysis of coupling constants, interproton distances, chemical shifts, and kinetics of amide exchange. Overall, the secondary structure of this PLA2 is similar to the **crystal** structure of the homologous group Gelb, M.H. and Sigler, P.B. (1991) Science, 254, 1007-1010). In the group I enzyme from porcine pancreas, the amino-terminal helix becomes fully ordered in the ternary complex of enzyme, lipid micelles and inhibitor. The formation of this helix is thought to be important for the increase in activity of phospholipases on aggregated substrates (Van den Berg, B., Tessari, M., Boelens, R., Dijkman. R., De Haas, G.H., Kaptein, R. and Verheij, H.M. (1995) Nature Struct. Biol., 2, 402-406). However. the group II enzyme from Agkistrodon piscivorus piscivorus possesses a defined and well-positioned amino-terminal helix in the absence of substrate. Therefore, there is a clear difference between the conformations of group I and group II enzymes in solution. These conformational differences suggest that formation of the amino-terminal helix is a necessary, but not sufficient, step in interfacial activation of phospholipases.

L37 ANSWER 53 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:297539 BIOSIS
DOCUMENT NUMBER: PREV199396015764
TITLE: An examination of structural interactions presumed to be of importance in the stabilization of phospholipase A-2 dimers based upon comparative protein sequence analysis of a monomeric and dimeric enzyme from the venom of Agkistrodon piscivorus piscivorus.
AUTHOR(S): Welches, William (1); Reardon, Ilene; Heinrikson, Robert L.
CORPORATE SOURCE: (1) Dep. Brain Vascular Res., Res. Div., NC3-149, Cleveland Clin. Foundation, 9500 Euclid Ave., Cleveland, OH 44195 USA
SOURCE: Journal of Protein Chemistry, (1993) Vol. 12, No. 2, pp. 187-193.
ISSN: 0277-8033.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Phospholipases A-2 may exist in solution both as monomers and dimers, but enzymes that form strong dimers (K-D approximately 10-9 M) have been found, thus far, only in venoms of the snake family Crotilidae. The complete amino acid sequences of a basic monomeric and an acidic dimeric phospholipase A-2 from Agkistrodon piscivorus piscivorus (American cotton-mouth water moccasin) venom have been determined by protein sequencing methods as part of a search for aspects of structure contributing to formation of stable dimers. Both the monomeric and dimeric phospholipases A-2 are highly homologous to the dimeric phospholipases A-2 from Crotalus atrox and Crotalus adamanteus venoms, and both have the seven residue carboxy-terminal extension characteristic of the crotalid and viperid enzymes. Thus, it is clear that the extension is not a prerequisite for dimerization. Studies to date have revealed two characteristic features of phosphilipases A-2 that exist in solution as strong dimers. One is the presence in the dimers of a Pro-Pro sequence at position 112 and 113 which just precedes the seven residue carboxy-terminal extension (residues 116-122). The other is a low isoelectric point; only the acidic phospholipases A-2 have been observed,

thus far, to form stable dimers. These, alone or together, may be necessary, though not sufficient conditions for phospholipase A-2 dimer formation. Ideas regarding subunit interactions based upon **crystallographic** data are evaluated relative to the new sequence information on the monomeric and dimeric phospholipases A-2 from A. p. piscivorus venom.

L37 ANSWER 54 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1991:90388 BIOSIS
DOCUMENT NUMBER: BA91:49278
TITLE: STRUCTURE OF AN ENGINEERED PORCINE PHOSPHOLIPASE A-2 WITH ENHANCED ACTIVITY AT 2.1 A RESOLUTION COMPARISON WITH THE WILD-TYPE PORCINE AND CROTALUS-ATROX PHOSPHOLIPASE A-2.
AUTHOR(S): THUNNISSEN M M G M; KALK K H; DRENTH J; DIJKSTRA B W
CORPORATE SOURCE: LAB. CHEM. PHYS., UNIV. GRONINGEN, NIJENBORG 16, 9747 AG GRONINGEN, NETHERLANDS.
SOURCE: J MOL BIOL, (1990) 216 (2), 425-440.
CODEN: JMOBAK. ISSN: 0022-2836.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The **crystal** structure of an engineered phospholipase A2 with enhanced activity has been refined to an R-factor of 18.6% at 2.1 .ANG. resolution using a combination of molecular dynamics refinement by the GROMOS package and least-squares refinement by TNT. This mutant phospholipase was obtained previously by deleting residues 62 to 66 in porcine pancreatic phospholipase A2, and changing Asp59 to Ser, Ser60 to Gly and Asn67 to Tyr. The refined structure allowed a detailed comparison with wild-type porcine and Crotalus atrox phospholipase A2. The conformation of the deletion region appears to be intermediate between that in those two enzymes. The residues in the active center are virtually the same. An internal hydrophobic are occupied by Phe63 in the wild-type porcine phospholipase A2 is kept as conserved as possible by local rearrangement of neighboring atoms. In the mutant structure, this hydrophobic pocket is now occupied by the disulfide bond between residues 61 and 91. A detailed description of the second binding site for a calcium ion in this enzyme is given.

L37 ANSWER 55 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1991:247637 BIOSIS
DOCUMENT NUMBER: BA91:128192
TITLE: PORCINE PANCREATIC PHOSPHOLIPASE A-2 SEQUENCE-SPECIFIC PROTON AND NITROGEN-15 NMR ASSIGNMENTS AND SECONDARY STRUCTURE.
AUTHOR(S): DEKKER N; PETERS A R; SLOTBOOM A J; BOELENS R; KAPTEIN R; DE HAAS G
CORPORATE SOURCE: BIJVOET CENTER BIOMOLECULAR RES., STATE UNIV. UTRECHT, P.O. BOX 80.054, 3584 CH UTRECHT, NETH.
SOURCE: BIOCHEMISTRY, (1991) 30 (12), 3135-3146.
CODEN: BICHAW. ISSN: 0006-2960.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The solution structure of porcine pancreatic phospholipase A2 (124 residues, 14 kDa) has been studied by two-dimensional homonuclear 1H and two- and three-dimensional heteronuclear 15N-1H nuclear magnetic resonance spectroscopy. Backbone assignments were made for 117 of the 124 amino acids. Short-range nuclear Overhauser effect (NOE) data show three .alpha.-helices from residues 1-13, 40-58, and 90-109, an antiparallel .beta.-sheet for residues 74-85, and a small antiparallel .beta.-sheet between residues 25-26 and 115-116. A15N-1H heteronuclear multiple-quantum correlation experiment was used to monitor amide proton exchange over a period of 22 h. In total 61 amide protons showed slow or intermediate exchange, 46 of which are located in the three large helices. Helix 90-109 was found to be considerably more stable than the other helices. For the .beta.-sheets, four hydrogen bonds could be identified. The secondary structure of porcine PLA in solution, as deduced from NMR, is basically the same as the structure fo porcine PLA in the **crystalline** state. Differences were found in the following regions, however. Residues 1-6 in the first .alpha.-helix are less structured in solution than in the **crystal** structure. Whereas in the **crystal** structure residues 24-29 are involved both in .beta.-sheet with residues 115-117 and in a hairpin turn, the expected

hydrogen bonds between residues 24-117 and 25-29 do not show slow exchange behavior. This and the absence of several expected NOEs imply that this region has a less well defined structure in solution. Finally, the hydrogen bond between residues 78-81, which is part of a .beta.-sheet, does not show slow exchange behavior.

L37 ANSWER 56 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1989:122501 BIOSIS
DOCUMENT NUMBER: BA87:57154
TITLE: EFFECT OF SELECTIVE CHEMICAL MODIFICATION AND CYANOGEN BROMIDE CLEAVAGE AT METHIONINE-20 ON CATALYTIC ACTIVITY AND SUBSTRATE BINDING PROPERTIES OF PORCINE PANCREATIC PHOSPHOLIPASE A-2.
AUTHOR(S): VAN DER WIELE F C; DEKKER N; VAN SCHARRENBURG G J M; HARTSKEERL R A; MEIJER H; DE HAAS G H; VAN DEENEN L L M; SLOTBOOM A J
CORPORATE SOURCE: LAB. BIOCHEM., STATE UNIV. UTRECHT, TRANSITORIUM III, UNIV. CENT. DE UITHOF, PADUALAAN 8, 3584 CH UTRECHT, NETH.
SOURCE: BIOCHIMIE (PARIS), (1988) 70 (9), 1215-1222.
CODEN: BICMBE. ISSN: 0300-9084.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Porcine pancreatic phospholipase A2 contains 2 methionine (Met) residues located at positions 8 and 20, respectively. Reaction of the enzyme with methyliodide and iodoacetic acid resulted in the selective methylation and carboxymethylation, respectively, of Met20. It was found that porcine pancreatic iso-phospholipase A2, possessing only Met8, was not affected by either modification. Reaction of porcine phospholipase A2 with cyanogen bromide in 0.1 N hydrochloric acid gave rise to cleavage only at Met20. The enhanced reactivity of Met20 compared to that of Met8 is in agreement with the known **X-ray** structure of phospholipase A2 which shows that Met8 is located in the interior of the protein, while Met20 is at the surface. Both methylation and carboxymethylation of Met20 do not significantly affect catalytic and substrate binding properties of the enzyme. In contrast, the more rigorous cleavage at Met20 by CNBr resulted in the loss of catalytic activity, while substrate and Ca2+ binding was diminished only to a limited extent. Most likely CNBr cleavage at Met20 perturbs the active site despite the fact that the N-terminal fragment Ala1-Hse20 is still bound via the disulfide bridge Cys11-Cys77 to the remainder of the protein. The results obtained strongly suggest that the conformation of the sequences Ala1-Hse20 and/or Asp21-Gly26 are important for the maintenance of the special microenvironment of the active site cleft.

L37 ANSWER 57 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:1607 BIOSIS
DOCUMENT NUMBER: PREV200000001607
TITLE: Structure of cadmium-substituted phospholipase A2 from Agkistrodon halys Pallas at 2.8ANG resolution.
AUTHOR(S): Zhang, Hailong (1); Zhang, Yaqun (1); Song, Shiying (1); Zhou, Yuancong; Lin, Zhengjiong
CORPORATE SOURCE: (1) National Laboratory of Biomacromolecules, Institute of Biophysics, Academia Sinica, Beijing, 100101 China
SOURCE: Protein and Peptide Letters, (Aug., 1999) Vol. 6, No. 4, pp. 185-193.
ISSN: 0929-8665.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The **crystal** structure of cadmium-substituted basic PLA2 from Agkistrodon halys Pallas (Agkistrodon blomhoffii Brevicaudus, A. h. Pallas) has been determined to 2.8 ANG with an R factor of 20.1%. Two cadmium-binding sites were found in the enzyme, one is near His48 (S1), the other is near Asp122 (S2). The ligand geometry of the metal ions is described and the inhibition of the catalytic activity by the metal ion is discussed.

L37 ANSWER 58 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:134878 BIOSIS
DOCUMENT NUMBER: PREV199900134878
TITLE: **Crystal** structure of a hemolytic toxin from

Agkistrodon halys Pallas at high resolution.
AUTHOR(S): Zhao, Ke-Hao; Song, Shi-Ying (1); Lin, Zheng-Jiong; Zhou, Yuan-Cong (1)
CORPORATE SOURCE: (1) National Lab. Biomacromol., Inst. Biophysics, Academia Sinica, Beijing 100101 China
SOURCE: Journal of Toxicology Toxin Reviews, (Nov., 1998) Vol. 17, No. 4, pp. 554.
Meeting Info.: Meeting of the Chinese Toxicological Society Nanning, Guangxi, China June 1997 Chinese Toxicological Society
. ISSN: 0731-3837.
DOCUMENT TYPE: Conference
LANGUAGE: English

L37 ANSWER 59 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:390104 BIOSIS
DOCUMENT NUMBER: PREV199800390104
TITLE: Structure of a basic phospholipase A2 from Agkistrodon halys Pallas at 2.13 A resolution.
AUTHOR(S): Zhao, Kehao (1); Song, Shiying (1); Lin, Zhengjion (1); Zhou, Yunacong
CORPORATE SOURCE: (1) Natl. Lab. Biomacromolecules, Inst. Biophysics, Academia Sinica, Beijing 10010 China
SOURCE: Acta Crystallographica Section D Biological Crystallography, (July 1, 1998) Vol. 54, No. 4, pp. 510-521.
ISSN: 0907-4449.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The basic phospholipase A2 isolated from the venom of Agkistrodon halys Pallas (Agkistrodon blomhoffii Brevicaudus) is a hemolytic toxin and one of the few PLA2's capable of hydrolyzing the phospholipids of E. coli membranes in the presence of a bactericidal/permeability-increasing protein (BPI) of neutrophils. The **crystal** structure has been determined and refined at 2.13 ANG to a R factor of 16.5% (F > 3sigma) with excellent stereochemistry. A superposition of the two molecules in the asymmetric unit gives an r.m.s. deviation of 0.326 ANG for all Calpha atoms. The refined structure allowed a detailed comparison with other PLA2 species of known structures. The overall architecture is similar to those of other PLA2'S with a few significant differences. One of which is in the region connecting the N-terminal helix and the Ca2+-binding loop. Unexpectedly, the conformation of the peptide plane Cys29-Gly30 in the Ca2+-binding loop is very different to that of other PLA2's. The amide NH of Gly30 does not point toward the proposed site for stabilization of the tetrahedral intermediate oxyanion of the substrate analogue. The structure includes four residues which occur less frequently in other PLA2's. His1, Arg6 and Trp70 located at the interfacial recognition site may play an important role in the interaction with aggregated substrates, while Trp77 contributes to the hydrophobic interactions between the beta-wing and the main body of the molecule. This structure analysis reveals that two clusters of basic residues are located at or near the interfacial recognition site, forming an asymmetric positively charge distribution. In contrast to the acidic isoform, the present enzyme is a dimer in the **crystalline** state. The special phospholipid hydrolysis behaviors are discussed in the light of the structure determined.

L37 ANSWER 60 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1992:3838 BIOSIS
DOCUMENT NUMBER: BA93:3838
TITLE: **CRYSTALLOGRAPHIC** REFINEMENT OF BOVINE PRO-PHOSPHOLIPASE A-2 AT 1.6 A RESOLUTION.
AUTHOR(S): FINZEL B C; WEBER P C; OHLENDORF D H; SALEMME F R
CORPORATE SOURCE: PHYSICAL ANALYTICAL CHEM., THE UPJOHN COMPANY, 301 HENRIETTA STREET, KALAMAZOO, MICH. 49001.
SOURCE: ACTA CRYSTALLOGR SECT B STRUCT SCI, (1991) 47 (5), 814-816.
CODEN: ASBSDK. ISSN: 0108-7681.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Bovine pro-phospholipase A2 (Mr = 14,520), trigonal, P3121, a = b = 46.5, c = 102.0 .ANG., one molecule per asymmetric unit, .lambda. (Cu K.alpha.) = 1.54 .ANG.. The model incorporating 895 protein atoms, two molecules of

2-methy-2,4-pentane-diol, and 60 solvent water molecules, was refined by restrained least squares to a residual R = 0.194 for 14,667 reflections from 5 to 1.6 .ANG. resolution.

L37 ANSWER 61 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:218974 BIOSIS
DOCUMENT NUMBER: PREV199900218974
TITLE: Evidence for a regulatory role of cholesterol superlattices in the hydrolytic activity of secretory phospholipase A2 in lipid membranes.
AUTHOR(S): Liu, Fang; Chong, Parkson Lee-Gau (1)
CORPORATE SOURCE: (1) Department of Biochemistry, Temple University School of Medicine, Philadelphia, PA, 19140 USA
SOURCE: Biochemistry, (March 30, 1999) Vol. 38, No. 13, pp. 3867-3873.
ISSN: 0006-2960.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have conducted a detailed study of the effect of membrane cholesterol content on the initial hydrolytic activity of Crotalus durissus terrificus venom phospholipase A2 (sPLA2) in large unilamellar vesicles of cholesterol/dimyristoyl-L-alpha-phosphatidylcholine (DMPC) and cholesterol/1-palmitoyl-2-oleoyl-L-alpha-phosphatidylcholine (POPC) at 37 degreeC. The activity was monitored by using the acrylodan-labeled intestinal fatty acid binding protein and HPLC. In contrast to conventional approaches, we have used small cholesterol concentration increments (apprx0.3-1.0 mol %) over a wide concentration range (e.g., 13-54 mol % cholesterol). In both membrane systems examined, the initial hydrolytic activity of sPLA2 is found to change with cholesterol content in an alternating manner. The activity reaches a local minimum when the membrane cholesterol content is at or near the critical cholesterol mole fractions (e.g., 14.3, 15.4, 20.0, 22.2, 25.0, 33.3, 40.0, and 50.0 mol % cholesterol) predicted for cholesterol regularly distributed in either hexagonal or centered rectangular superlattices. According to the sterol regular distribution model (Chong, P. L.-G. (1994) Proc. Natl. Acad. Sci. U.S.A. 91, 10069-10073; Liu et al. (1997) Biophys. J. 72, 2243-2254), the extent of lipid superlattices is maximal at the critical cholesterol mole fractions, at which the membrane free volume is minimal. Thus, our present data can be taken to indicate that the initial hydrolytic activity of sPLA2 is governed by the extent of cholesterol superlattice. These data provide the first functional evidence for the formation of cholesterol superlattices in both saturated (e.g., DMPC) and unsaturated (e.g., POPC) liquid-**crystalline** phospholipid bilayers. The data also illustrate the functional importance of cholesterol superlattice and demonstrate a new type of regulation of sPLA2. Furthermore, upon binding to cholesterol/POPC large unilamellar vesicles, the intrinsic fluorescence intensity of sPLA2 shows an alternating variation with cholesterol content, exhibiting a minimum at the critical cholesterol mole fractions. This result suggests that either the number of sPLA2 bound to lipid vesicles or the conformation of membrane-bound sPLA2 or both vary with the extent of the cholesterol superlattice in the plane of the membrane.

L37 ANSWER 62 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:180308 BIOSIS
DOCUMENT NUMBER: PREV199900180308
TITLE: Structural analysis of phospholipase A2 from functional perspective. 1. Functionally relevant solution structure and roles of the hydrogen-bonding network.
AUTHOR(S): Yuan, Chunhua; Byeon, In-Ja L.; Li, Yishan; Tsai, Ming-Daw (1)
CORPORATE SOURCE: (1) Department of Chemistry, Ohio State University, 100 West 18th Avenue, Columbus, OH, 43210-1173 USA
SOURCE: Biochemistry, (March 9, 1999) Vol. 38, No. 10, pp. 2909-2918.
ISSN: 0006-2960.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Bovine pancreatic phospholipase A2 (PLA2), a small (13.8 kDa) Ca2+-dependent lipolytic enzyme, is rich in functional and structural character. In an effort to examine its detailed structure-function

relationship, we determined its solution structure by multidimensional nuclear magnetic resonance (NMR) spectroscopy at a functionally relevant pH. An ensemble of 20 structures generated has an average root-mean-square deviation (RMSD) of 0.62 +- 0.08 ANG for backbone (N, Calpha, C) atoms and 0.98 +- 0.09 ANG for all heavy atoms. The overall structure shows several notable differences from the **crystal** structure: the first three residues at the N-terminus, the calcium-binding loop (Y25-T36), and the surface loop (V63-N72) appear to be flexible; the alpha-helical conformation of helix B (E17-F22) is absent; helix D appears to be shorter (D59-V63 instead of D59-D66); and the hydrogen-bonding network is less defined. These differences were analyzed in relation to the function of PLA2. We thenfurther examined the H-bonding network, because its functional role or even its existence in solution has been in dispute recently. Our results show that part of the H-bonding network (the portion away from N-terminus) clearly exists in solution, as evidenced by direct observation (at 11.1 ppm) of a strong H-bond between Y73 and D99 and an implicated interaction between D99 and H48. Analyses of a series of mutants indicated that the existence of the Y73cntdotcntdotcntdotD99 H-bond correlates directly with the conformational stability of the mutant. Loss of this H-bond results in a loss of 2-3 kcal/mol in the conformational stability of PLA2. The unequivocal identification and demonstration of the structural importance of a specific hydrogen bond, and the magnitude of its contribution to conformational stability, are uncommon to the best of our knowledge. Our results also suggest that, while the D99cntdotcntdotcntdotH48 catalytic diad is the key catalytic machinery of PLA2, it also helps to maintain conformat ional integrity.

L37 ANSWER 63 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:477102 BIOSIS
DOCUMENT NUMBER: PREV199396110702
TITLE: Molecular dynamics simulation of 1,2-dilauroyl-L-phosphatidylethanolamine binding to phospholipase A-2: An attempt to explain the selective hydrolysis of substrate fatty acid ester at position 2.
AUTHOR(S): Ohishi, Hirofumi (1); Fujii, Shinobu (1); Tomoo, Koji (1); Ishida, Toshimasa (1); Ikeda, Kiyoshi (1); Tanabe, Kazutoshi; Kitamura, Kunihiro
CORPORATE SOURCE: (1) Osaka University Pharmaceutical Sci., 2-10-65 Kawai, Matsubara, Osaka 580
SOURCE: Journal of Biochemistry (Tokyo), (1993) Vol. 114, No. 2, pp. 210-214.
ISSN: 0021-924X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB To improve our understanding of why phospholipase A-2 (PLA-2) specifically catalyzes the hydrolysis of the fatty acid ester bond at position 2, not at position 1, of 1,2-diacyl-3-sn-phosphoglycerides, the binding of each fatty acid chain of 1,2-dilauroyl-L-phosphatidyl-ethanolamine (DLPE), a natural substrate, to bovine pancreas PLA-2 was examined by molecular dynamics (MD) simulations. Two different binding modes were considered, i.e., the respective hydrocarbon chains of 1- and 2-lauroyl fatty acid esters were located at the PLA-2 binding sites usually observed in the complex **crystals** (Form A2) and at the reverse sites (Form A1). Although the total energies of both forms fluctuated within nearly the same range during the 80 ps MD simulations, the binding mode of DLPE to the PLA-2 catalytic site through the coordination of Ca-2+ was much more advantageous in Form A2 than that in Form A1; significant deviation of the Ca-2+ position from its starting structure was observed in the MD simulation of Form A1. The result suggests the importance of Ca-2+ in the selective recognition and catalytic function of PLA-2 toward the 2-positioned fatty acid ester of phosphoglyceride substrates.

L37 ANSWER 64 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:341151 BIOSIS
DOCUMENT NUMBER: PREV199396038151
TITLE: Phosphatidylcholine as substrate for human pancreatic phospholipase A-2: Importance of the physical state of the substrate.
AUTHOR(S): Borgstrom, Bengt
CORPORATE SOURCE: P.O. Box 94, S-221 00 Lund Sweden
SOURCE: Lipids, (1993) Vol. 28, No. 5, pp. 371-375.

ISSN: 0024-4201.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The long-chain phosphatidylcholine/sodium cholate aqueous system as substrate for human pancreatic phospholipase A-2 (PLA-2) was investigated. At a constant phosphatidycholine (PC) concentration of 8 mM, the enzyme activity increased with a decrease in cholate (C) concentration up to a PC/C ratio of approximately 0.8 and then rather abruptly decreased to lower values at a ratio above 1.5. At ratios between 0.8 and 1.5, an increasing lag phase in the PLA-2 activity was seen, indicating a progressive decrease in substrate availability to the enzyme. Reaction mixtures with a PC/C ratio of up to 0.67 were optically clear solutions composed of mixed bile salt/PC micelles of increasing mixed micellar aggregate size. Ratios between 0.67 and 1.5 were characterized by an increase in turbidity (at 330 and 450 nm) due to increasing formation of vesicles or liposomes. Above a PC/C ratio of 1.5, a sharp increase in turbidity was seen due to increasing formation of bilayer structures other than vesicles. Pure vesicles obtained by dialysis of mixed micellar solutions were not hydrolyzed by the enzyme. Addition of bile salts reversed the inhibition which was accompanied by a decrease in turbidity. Phosphatidylcholine was preferred as substrate for human PLA-2 when present in large mixed disc-like bile salt micelles. Vesicular or other types of lamellar liquid-**crystalline** phases of long-chain phosphatidylcholine did not serve as substrate for PLA-2.

L37 ANSWER 65 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1989:446860 BIOSIS
DOCUMENT NUMBER: BA88:95132
TITLE: RAMAN AND IR STUDIES ON THE CONFORMATION OF PORCINE PANCREATIC AND CROTALUS-DURISSUS-TERRIFICUS PHOSPHOLIPASES A-2.
AUTHOR(S): AREAS E P G; LAURE C J; GABILAN N; ARAUJO P S; KAWANO Y
CORPORATE SOURCE: DEPARTAMENTO QUIMICA FUNDAMENTAL, ISTITUTO DE QUIMICA DA USP, CAIXA POSTAL 20780, CEP 01498, SAO PAULO SP, BRAZIL.
SOURCE: BIOCHIM BIOPHYS ACTA, (1989) 997 (1-2), 15-26.
CODEN: BBACAQ. ISSN: 0006-3002.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Raman and infrared spectroscopies were used to investigate conformational features of Crotalus durissus terrificus and porcine pancreatic phospholipases A2, as well as the proenzyme of the latter. The results indicate that conformational changes occur for the phospholipase molecules as a consequence of different experimental conditions such as change of physical state, presence of certain ionic species and interaction with a model substrate analog. Amorphous and **crystalline** solid phospholipase present discrepant conformational features. Conformational transitions were detected for the pancreatic zymogen .fwdarw. phospholipase A2 transformation and different secondary contents were observed for a toxic and a nontoxic form of the phospholipase molecule. All those structural changes have been shown to involve primarily the architecture of the polypeptide backbone rather than the conformation of amino acid residue side-chains. Disulfide bridges have shown consistently a gauche-gauche-gauche geometry which has not been disturbed by any of the experimental conditions employed. The external occurrence of tryptophan residues has been a common feature for the systems assayed, as well as the predominant localization of tyrosine residues in hydrophilic environment, probably at the molecular surface.

L37 ANSWER 66 OF 73 MEDLINE
ACCESSION NUMBER: 2000006229 MEDLINE
DOCUMENT NUMBER: 20006229 PubMed ID: 10535917
TITLE: A structural view of evolutionary divergence.
AUTHOR: Spiller B; Gershenson A; Arnold F H; Stevens R C
CORPORATE SOURCE: Department of Molecular Biology, University of California, Berkeley, CA 92037, USA.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Oct 26) 96 (22) 12305-10.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1C00; PDB-1QE3; PDB-1QE8
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991210

AB Two directed evolution experiments on p-nitrobenzyl esterase yielded one enzyme with a 100-fold increased activity in aqueous-organic solvents and another with a 17 degrees C increase in thermostability. Structures of the wild type and its organophilic and thermophilic counterparts are presented at resolutions of 1.5 A, 1.6 A, and 2.0 A, respectively. These structures identify groups of interacting mutations and demonstrate how directed evolution can traverse complex fitness landscapes. Early-generation mutations stabilize flexible loops not visible in the wild-type structure and set the stage for further beneficial mutations in later generations. The mutations exert their influence on the esterase structure over large distances, in a manner that would be difficult to predict. The loops with the largest structural changes generally are not the sites of mutations. Similarly, none of the seven amino acid substitutions in the organophile are in the active site, even though the enzyme experiences significant changes in the organization of this site. In addition to reduction of surface loop flexibility, thermostability in the evolved esterase results from altered core packing, helix stabilization, and the acquisition of surface salt bridges, in agreement with other comparative studies of mesophilic and thermophilic enzymes. **Crystallographic** analysis of the wild type and its evolved counterparts reveals networks of mutations that collectively reorganize the active site. Interestingly, the changes that led to diversity within the alpha/beta hydrolase enzyme family and the reorganization seen in this study result from main-chain movements.

L37 ANSWER 67 OF 73 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 88242897 EMBASE
DOCUMENT NUMBER: 1988242897
TITLE: Novel anti-inflammatory peptides from the region of highest similarity between uteroglobin and lipocortin I.
AUTHOR: Miele L.; Cordella-Miele E.; Facchiano A.; Mukherjee A.B.
CORPORATE SOURCE: Section on Developmental Genetics, Human Genetics Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892, United States
SOURCE: Nature, (1988) 335/6192 (726-730).
ISSN: 0028-0836 CODEN: NATUAS
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal
FILE SEGMENT: 030 Pharmacology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Significant future developments in the effective treatment of inflammatory diseases may arise from non-toxic dual inhibitors of both cyclooxygenase and lipoxygenase pathways in the arachidonate cascade. Inhibition of phospholipase A2 (PLA2) (**EC 3.1.1.4**), may provide such a dual action and recent research has concentrated on the role of PLA2-inhibitory proteins as possible anti-inflammatory agents. Blastokinin or uteroglobin is a steroid-induced rabbit secretory protein with PLA2-inhibitory activity. Its biochemical and biological properties have been extensively studied and its **crystallographic** structure has been resolved at 1.34 .ANG.. Lipocortins are a family of related proteins, which, it has been suggested, mediate the antiinflammatory effects of glucocorticoids. Some proteins of this group have been purified and the complementary DNA sequences of two human lipocortins are known. Lipocortins inhibit PLA2 in vitro, although their mechanism of action is still unclear. Recombinant lipocortin I inhibits eicosanoid synthesis in isolated perfused lungs from the guinea pig. Here, we report that synthetic oligopeptides corresponding to a region of high amino-acid sequence similarity between uteroglobin and lipocortin I have potent PLA2 inhibitory activity in vitro and striking anti-inflammatory effects in vivo.

L37 ANSWER 68 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)

ACCESSION NUMBER: 1999:850389 SCISEARCH
THE GENUINE ARTICLE: 251HX
TITLE: **Crystal** structure of the PTEN tumor suppressor: Implications for its phosphoinositide phosphatase activity and membrane association
AUTHOR: Lee J O; Yang H J; Georgescu M M; DiCristofano A; Maehama T; Shi Y G; Dixon J E; Pandolfi P; Pavletich N P (Reprint)
CORPORATE SOURCE: MEM SLOAN KETTERING CANC CTR, CELLULAR BIOCHEM & BIOPHYS PROGRAM, 1275 YORK AVE, NEW YORK, NY 10021 (Reprint); MEM SLOAN KETTERING CANC CTR, CELLULAR BIOCHEM & BIOPHYS PROGRAM, NEW YORK, NY 10021; MEM SLOAN KETTERING CANC CTR, HOWARD HUGHES MED INST, NEW YORK, NY 10021; MEM SLOAN KETTERING CANC CTR, DEPT HUMAN GENET, NEW YORK, NY 10021; MEM SLOAN KETTERING CANC CTR, PROGRAM MOL BIOL, NEW YORK, NY 10021; CORNELL UNIV, JOAN & SANFORD I WEILL GRAD SCH MED SCI, SLOAN KETTERING DIV, DEPT PHARMACOL, NEW YORK, NY 10021; ROCKEFELLER UNIV, MOL ONCOL LAB, NEW YORK, NY 10021; UNIV MICHIGAN, DEPT BIOL CHEM, ANN ARBOR, MI 48109; PRINCETON UNIV, DEPT MOL BIOL, PRINCETON, NJ 08544
COUNTRY OF AUTHOR: USA
SOURCE: CELL, (29 OCT 1999) Vol. 99, No. 3, pp. 323-334. Publisher: CELL PRESS, 1050 MASSACHUSETTES AVE, CIRCULATION DEPT, CAMBRIDGE, MA 02138. ISSN: 0092-8674.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 42

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The PTEN tumor suppressor is mutated in diverse human cancers and in hereditary cancer predisposition syndromes. PTEN is a phosphatase that can act on both polypeptide and phosphoinositide substrates in vitro. The PTEN structure reveals a phosphatase domain that is similar to protein phosphatases but has an enlarged active site important for the accommodation of the phosphoinositide substrate. The structure also reveals that PTEN has a C2 domain. The PTEN C2 domain binds phospholipid membranes in vitro, and mutation of basic residues that could mediate this reduces PTEN's membrane affinity and its ability to suppress the growth of glioblastoma tumor cells. The phosphatase and C2 domains associate across an extensive interface, suggesting that the C2 domain may serve to productively position the catalytic domain on the membrane.

L37 ANSWER 69 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:349372 BIOSIS
DOCUMENT NUMBER: PREV199396046372
TITLE: Inorganic pyrophosphatase of clofibrate-induced rat liver peroxisomes.
AUTHOR(S): Shimizu, Sakae; Ohkuma, Shoji (1)
CORPORATE SOURCE: (1) Dep. Biochemistry, Faculty Pharmaceutical Sciences, Kanazawa Univ., 13-1 Takara-machi, Kanazawa, Ishikawa 920 Japan
SOURCE: Journal of Biochemistry (Tokyo), (1993) Vol. 113, No. 4, pp. 462-466. ISSN: 0021-924X.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Clofibrate increased inorganic pyrophosphatase (PPase) activity in peroxisomes more than 12-fold (740 milliunits/head, 15.9 +- 5.0 milliunits/mg protein) in rat liver. The distribution of cytochrome c oxidase and that of the PPase in a Nycodenz gradient suggested that the PPase is an original peroxisomal enzyme and not a mitochondrial contaminant: This was confirmed by second Nycodenz gradient centrifugation. The optimum pH of the peroxisomal PPase was about 8.5. The activity was specific to inorganic pyrophosphate (PP-i), the K-m value for PP-i being 34.1 +- 3.3 mu-M. It was strictly dependent on Mg-2+ and showed a sigmoidal dose-response for Mg-2+ with an S-0.5 value of 100 mu-M. The activity was inhibited by Ca-2+, p-chloromercuriphenylsulfonic acid, Hg-2+, N-ethylmaleimide, and NaF. The functions of peroxisomal PPase are discussed.

L37 ANSWER 70 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)

ACCESSION NUMBER: 1999:478642 SCISEARCH
THE GENUINE ARTICLE: 207DE
TITLE: Annexin V and phospholipid metabolism
AUTHOR: RussoMarie F (Reprint)
CORPORATE SOURCE: INSERM, INST COCHIN GENET MOL, U332, 22 RUE MECHAIN, F-75014 PARIS, FRANCE (Reprint)
COUNTRY OF AUTHOR: FRANCE
SOURCE: CLINICAL CHEMISTRY AND LABORATORY MEDICINE, (MAR 1999) Vol. 37, No. 3, pp. 287-291.
Publisher: WALTER DE GRUYTER & CO, GENTHINER STRASSE 13, D-10785 BERLIN, GERMANY.
ISSN: 1434-6621.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 36

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Annexins, protein kinases C and cytosolic phospholipase A, belong to three families of ubiquitous cytoplasmic proteins involved in signal transduction. All annexins share the property of binding to phospholipids in the presence of calcium. Most annexins are sub strates for protein kinases C except annexin V,the most ubiquitous and abundant annexin. Protein kinases C (PKC) belong to three distinct groups of kinases, conventional PKCs (cPKCs) that depend on calcium, diacylglycerol and negatively charged phospholipids for their activity, novel PKCs (nPKCs) and atypical PKCs (aPKCs), that do not require calcium for their activity, although they both require negatively charged phospholipids. Cytosolic phospholipase A(2)? (**cPLA2**) depends on calcium for its catalytic activity as well as on serine phosphorylation by MAP kinases. Wt! report that annexin V modulates the activity of cPKCS as well as of **cPLA2** by interfering with their ability to bind to negatively charged phospholipids and calcium. We propose that annexin V could interfere with the calcium and phospholipid signalling pathway.

L37 ANSWER 71 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 94:267312 SCISEARCH
THE GENUINE ARTICLE: NK184
TITLE: DIVERSITY OF GROUP TYPES, REGULATION, AND FUNCTION OF PHOSPHOLIPASE A(2)
AUTHOR: DENNIS E A (Reprint)
CORPORATE SOURCE: UNIV CALIF SAN DIEGO, REVELLE COLL, CTR MOLEC GENET, DEPT CHEM 0601, LA JOLLA, CA, 92093 (Reprint); UNIV CALIF SAN DIEGO, SCH MED, LA JOLLA, CA, 92093
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (06 MAY 1994) Vol. 269, No. 18, pp. 13057-13060.
ISSN: 0021-9258.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 67

L37 ANSWER 72 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 94:217884 SCISEARCH
THE GENUINE ARTICLE: NF042
TITLE: INHIBITION OF HUMAN SECRETORY CLASS-II PHOSPHOLIPASE A(2) BY HEPARIN
AUTHOR: DUA R; CHO W (Reprint)
CORPORATE SOURCE: UNIV ILLINOIS, DEPT CHEM MC 111, 845 W TAYLOR ST, CHICAGO, IL, 60607 (Reprint); UNIV ILLINOIS, DEPT CHEM MC 111, CHICAGO, IL, 60607
COUNTRY OF AUTHOR: USA
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (01 APR 1994) Vol. 221, No. 1, pp. 481-490.
ISSN: 0014-2956.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 70

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB By means of kinetic analyses using Triton X-100/deoxycholic

acid/dilauroylglycerophosphoethanolamine (4:2:1, molar ratio) mixed micelles we examined the effects of heparin on the activity of several phospholipases A(2) (PLA(2)). Heparin avidly bound cationic PLA(2)s including human secretory class II PLA(2) and thereby inhibited their hydrolysis of phospholipids in the mixed micelles. Initial velocity measurements indicated that heparin behaved as a competitive inhibitor for human secretory class II PLA(2) and closely related A.h. blomhoffii PLA, and A.p. piscivorus PLA(2). In particular, heparin showed the highest specificity for human secretory class II PLA(2). In the absence of deoxycholic acid in mixed micelles, A.h. blomhoffii PLA(2) was also strongly inhibited by heparin. The observed inhibition was not due to the interaction of heparin with the active site of PLA(2) because heparin did not inhibit the hydrolysis of monomeric substrates by PLA(2)s. Both kinetic measurements and fluorescence measurements of PLA(2)-bound 8-anilino-1-naphthalene sulfonate in the presence of varying amounts of heparin showed that a heparin molecule bound about seven molecules of PLA(2). When positive charges of four lysines in the amino-terminal region of A.h. blomhoffii PLA(2) were neutralized by limited carbamoylation, heparin neither bound the carbamoylated A. h. blomhoffii PLA(2) nor inhibited the hydrolysis of Triton X-100/dilauroylglycerophosphocholine mixed micelles by the carbamoylated A.h. blomhoffii PLA(2) that retained 50% activity of native A.h. blomhoffii PLA(2). Also, heparin did not inhibit the hydrolysis of mixed micelles by 7,10-bis(octanoyl)ated A.p. piscivorus PLA(2) in which two lysines in the amino-terminal alpha-helix are acylated. These results indicate that the inhibition of human secretory class II PLA(2) and related cationic PLA(2)s by heparin Originates from the interaction of heparin with cationic residues in the aminoterminal region that forms a part of interfacial binding site. In addition, unique structural features of human secretory class II PLA(2), together with its unique mode of interaction with heparin, su that this PLA(2) might have an additional heparin-binding site. Although the heparin-PLA(2) binding diminished as the ionic strength of reaction medium increased, the inhibition of human secretory class II PLA(2) by heparin remained significant at the physiological ionic strength. An estimated value of inhibition constant (K-i) was 0.1 mu M under physiological conditions, which suggests that a normal pharmaceutical dose of heparin might inhibit human secretory class II PLA(2) and regulate its biological effects.

L37 ANSWER 73 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 92:482629 SCISEARCH
THE GENUINE ARTICLE: JH469
TITLE: DESIGN AND SYNTHESIS OF SOME SUBSTRATE-ANALOG INHIBITORS OF PHOSPHOLIPASE-A2 AND INVESTIGATIONS BY NMR AND MOLECULAR MODELING INTO THE BINDING INTERACTIONS IN THE ENZYME-INHIBITOR COMPLEX
AUTHOR: BENNION C; CONNOLLY S; GENSMANTEL N P; HALLAM C; JACKSON C G; PRIMROSE W U; ROBERTS G C K (Reprint); ROBINSON D H; SLAICH P K
CORPORATE SOURCE: UNIV LEICESTER, CTR BIOL NMR, LEICESTER LE1 7RH, ENGLAND; FISONS PLC, DIV PHARMACEUT, RES & DEV LABS, DEPT MED CHEM, LOUGHBOROUGH LE11 0RH, LEICS, ENGLAND; FISONS PLC, DIV PHARMACEUT, RES & DEV LABS, DEPT PHYS CHEM, LOUGHBOROUGH LE11 0RH, LEICS, ENGLAND; FISONS PLC, DIV PHARMACEUT, RES & DEV LABS, DEPT PHYS CHEM, LOUGHBOROUGH LE11 0RH, LEICS, ENGLAND; UNIV LEICESTER, DEPT BIOCHEM, LEICESTER LE1 7RH, ENGLAND
COUNTRY OF AUTHOR: ENGLAND
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (07 AUG 1992) Vol. 35, No. 16, pp. 2939-2951.
ISSN: 0022-2623.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 80
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A series of substrate analogue inhibitors of pancreatic phospholipase A2 has been designed and synthesized. The compounds were tested in a novel dual-screening system based on parallel assays with monomeric and micellar substrates. Intermolecular nuclear Overhauser effects between vinylic protons on one inhibitor and identified active site residues on the bovine

pancreatic enzyme have been observed in solution NMR studies of the enzyme-inhibitor complex. It can be deduced from both the biochemical results and the NMR data that the mode of interaction between this type of inhibitor and the active site of phospholipase A2 is essentially the same, irrespective of the presence or absence of an aggregated phospholipid surface. A model of the binding between the enzyme and inhibitor which incorporates the two-dimensional NMR data has been developed. The model can account for the activity of modified inhibitor structures and can be extrapolated to an assessment of the mode of binding of the natural substrate itself.

=> log y